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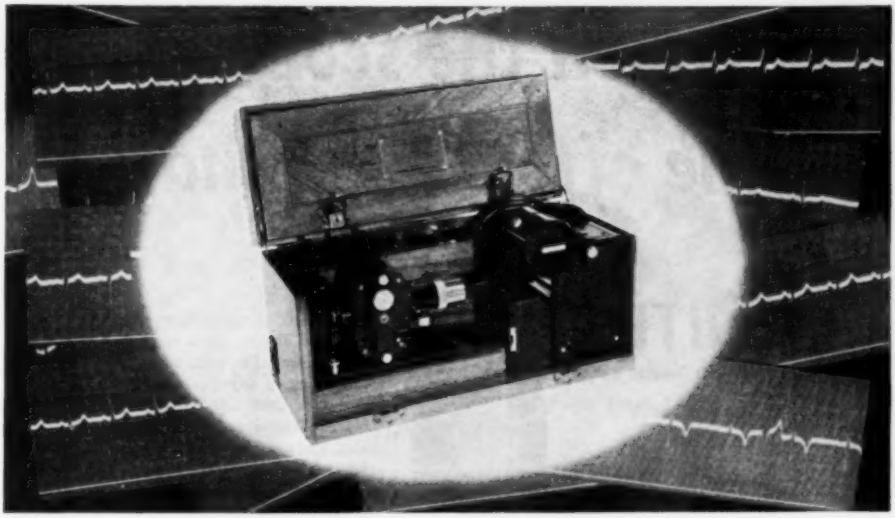

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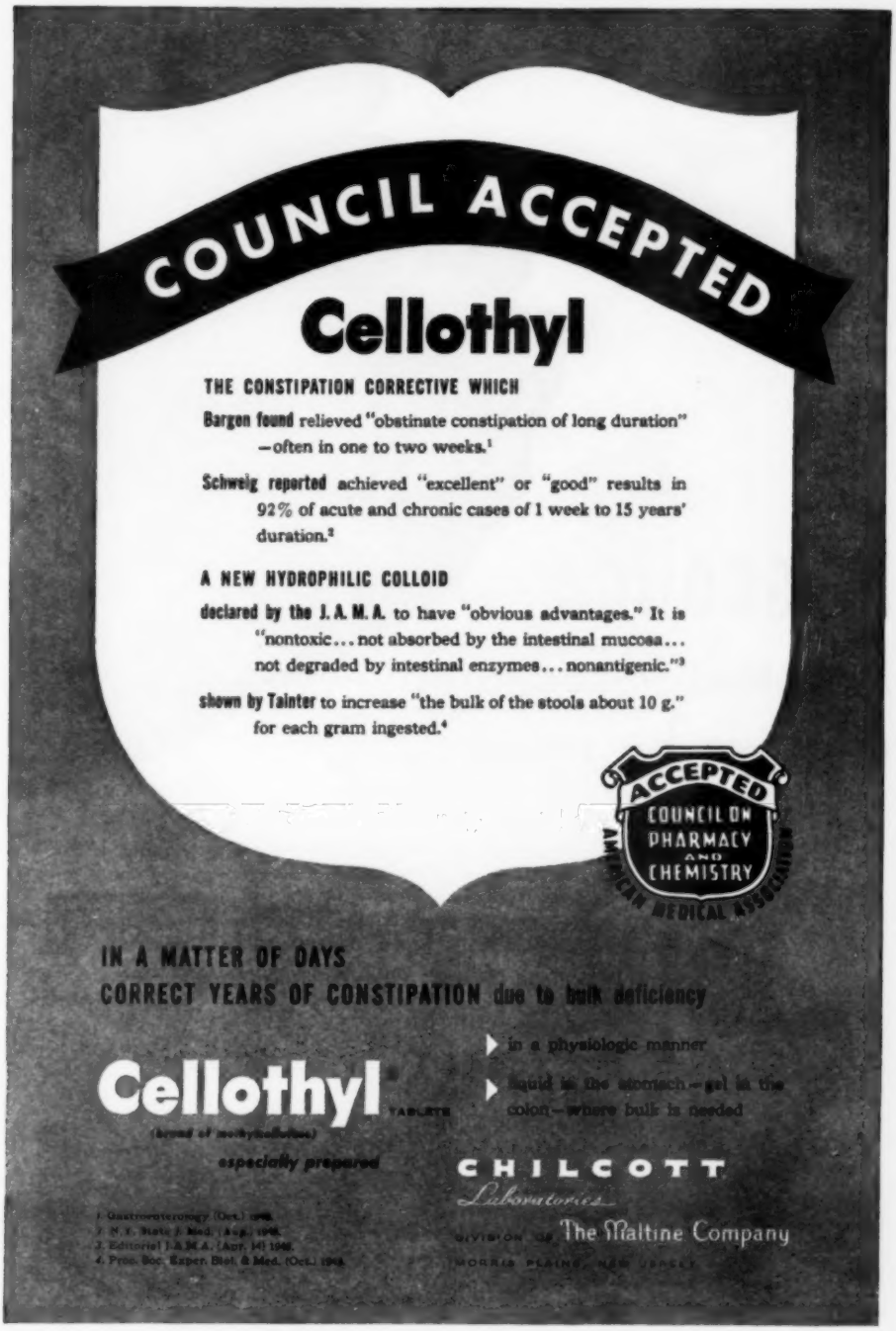
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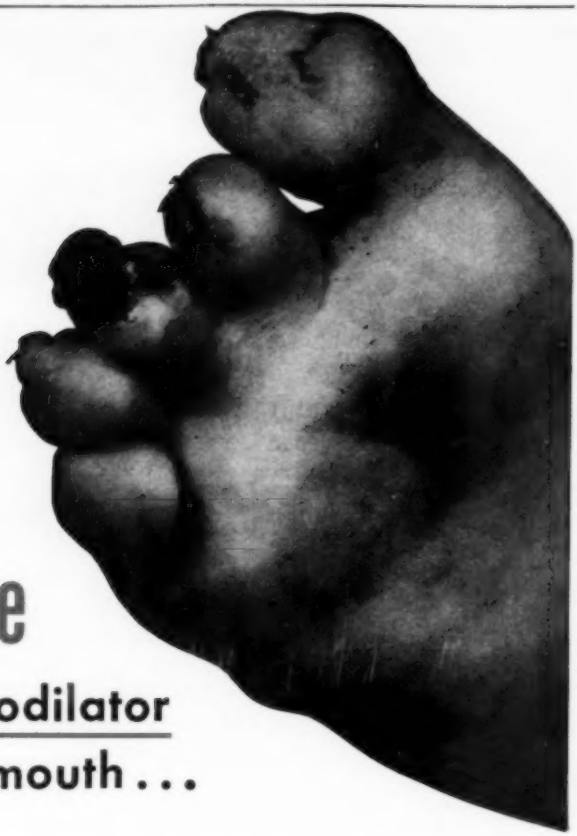
4. Proc. Soc. Exper. Biol. & Med. (Oct.) 1948.



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2. Wyatt, Bernard L.: Ann. West. Med. & Surg., Aug. 1949
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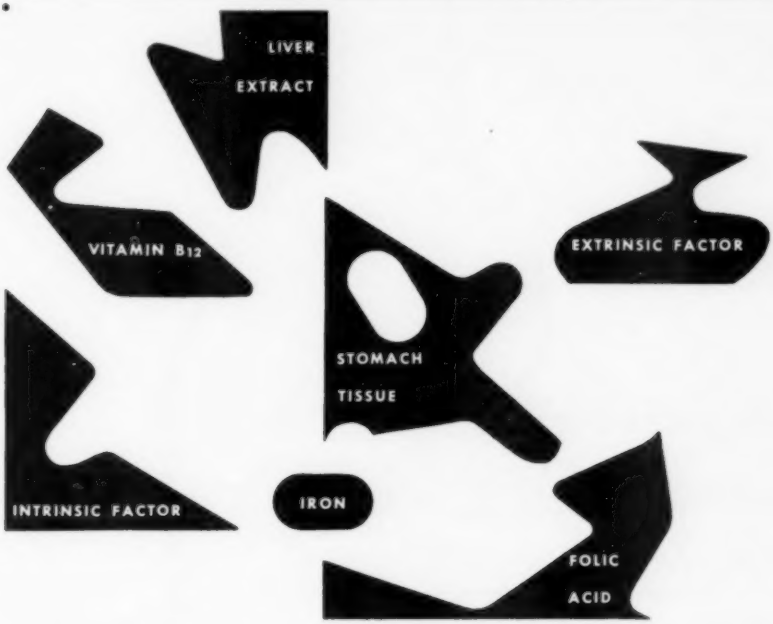

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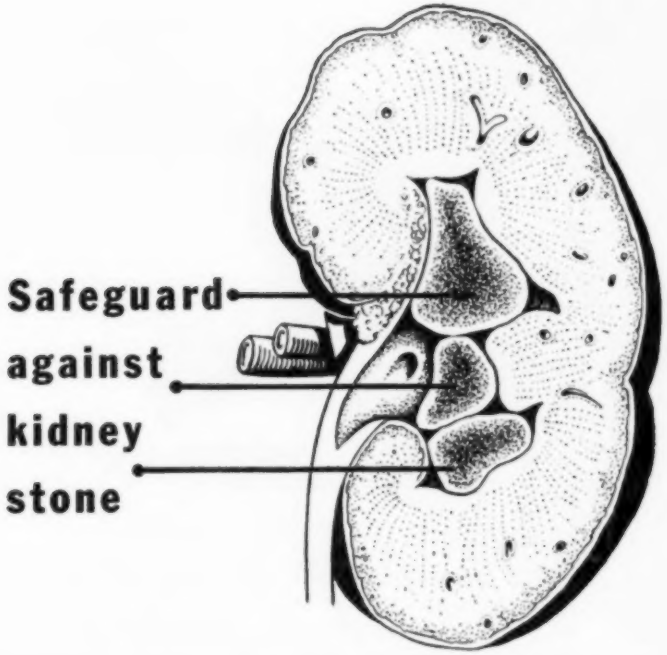

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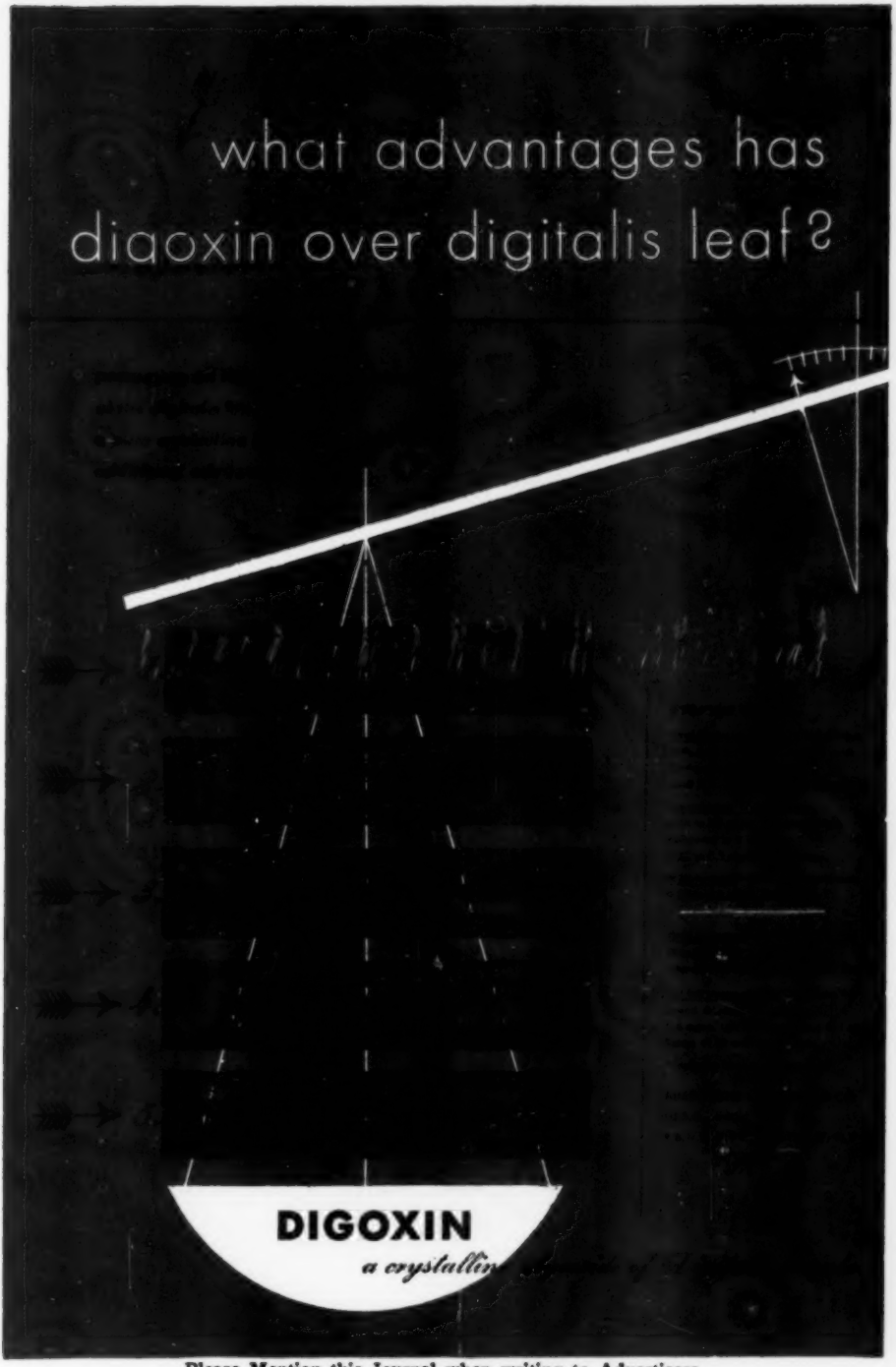

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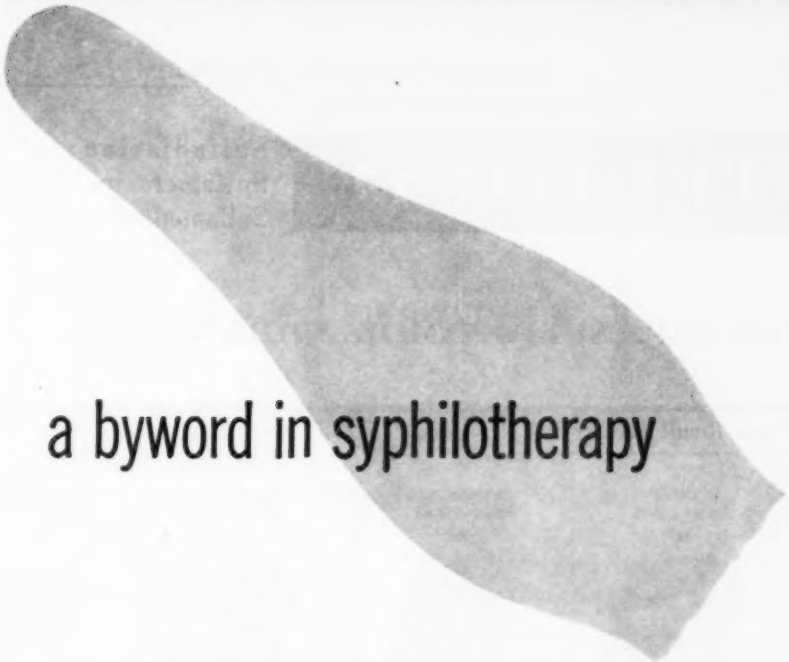

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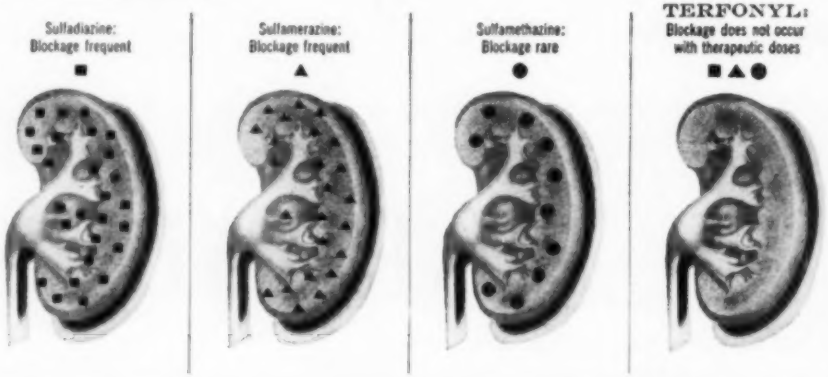

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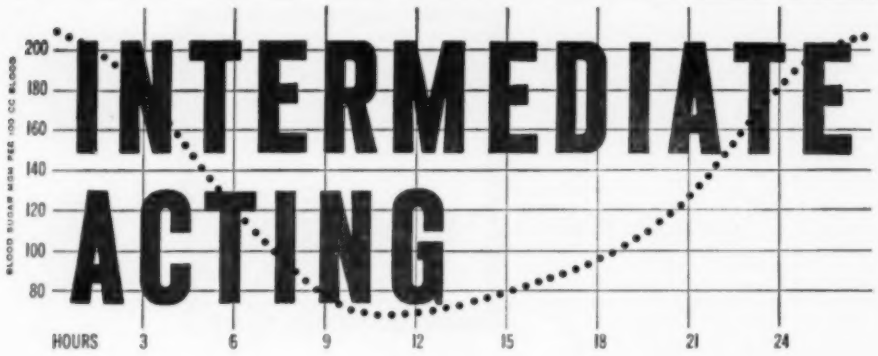

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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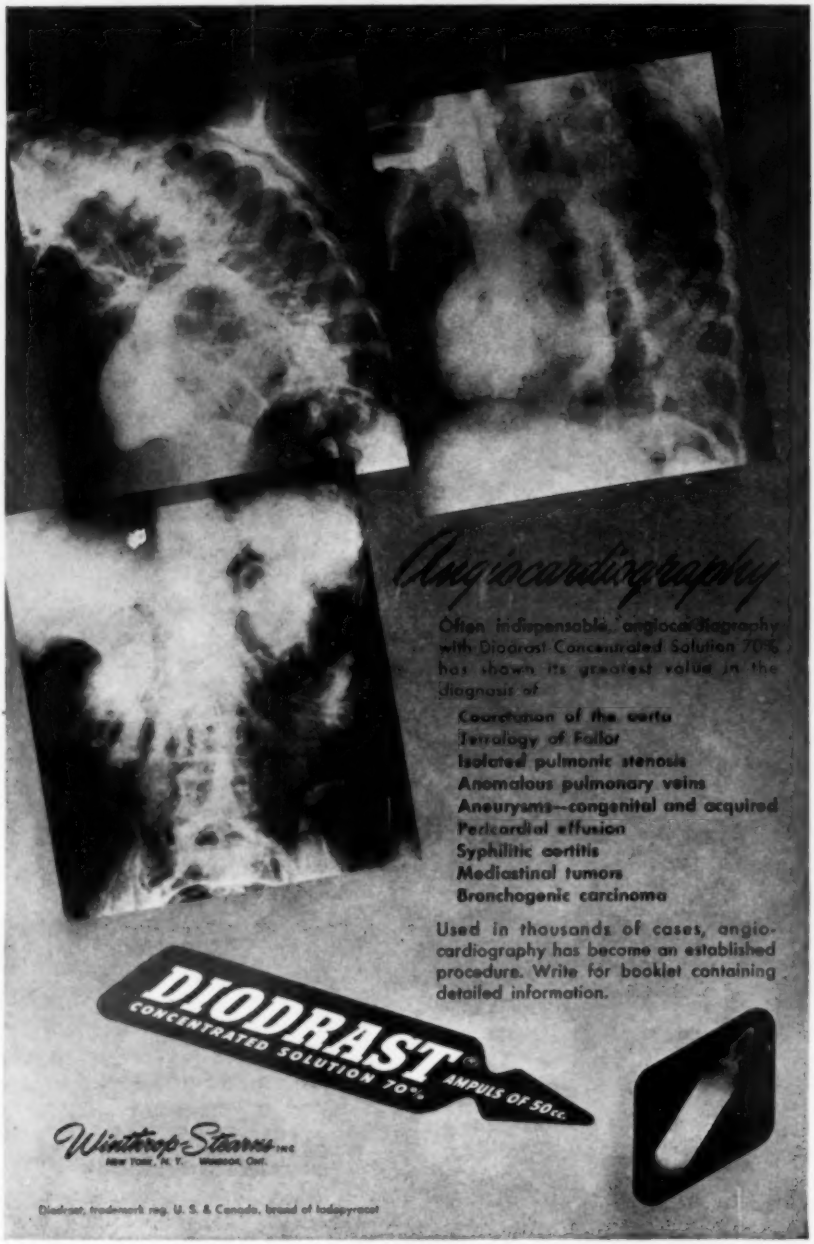
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**Alfred C. Beck, M.D., Obstetrical Practice, Fourth Edition, Chapter IX, Page 181, Published 1947 by The Williams & Wilkins Company, Baltimore*

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ANNALS OF
INTERNAL MEDICINE

VOLUME 32 MARCH, 1950 NUMBER 3

THE TREATMENT OF THE LYMPHOMAS AND OTHER NEOPLASTIC DISEASES WITH NITROGEN MUSTARD *

By LOUIS K. ALPERT, M.D., F.A.C.P., *Washington, D. C.*, EZRA M. GREENSPAN, M.D., *Baltimore, Maryland,* and STANLEY S. PETERSON, M.D., *Springfield, Missouri*

THE beta-chloroethyl amines, or nitrogen mustards, have been used since 1942 [1-7] in the treatment of lymphomas as well as a variety of miscellaneous malignancies. It appears that, although no malignancy has been eradicated by the use of these chemical agents, some degree of temporary control has been effected in the clinical course of patients with Hodgkin's disease, the lymphosarcomas, chronic leukemias, polycythemia vera, transitional cell carcinomas, and in certain undifferentiated carcinomas of the lung and testis. Remissions in symptoms and reduction in size of tumor masses have been achieved in a significant proportion of the patients with these diseases. However, in other malignant new growths such as melanosarcoma, multiple myeloma, metastatic mammary and cervical carcinoma and sympathicoblastoma, the nitrogen mustards have been of little value.

The relative effectiveness of the mustard compounds and roentgen-ray therapy is still being evaluated. In experimental studies it has been noted that the biological activities of the two agents are remarkably similar.[8, 9] In the clinical observations it appears that roentgen therapy is the treatment of choice when the lesions are well localized and readily accessible, whereas in patients with wide-spread and rapidly progressive disease, nitrogen mustard may be more effective in producing palliative results, even though these are temporary.

PHARMACOLOGY

The pharmacological activities of the nitrogen and sulfur mustards have been summarized by Gilman and Philips.[8] These substances have a potent

* Received for publication July 8, 1948.
From the Medical Service, Walter Reed General Hospital, Washington, D. C.

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cytotoxic effect on actively proliferating cells, the precise nature of which is still only partially explained. Among the changes in cellular metabolism which have been demonstrated are reduction in oxygen consumption, depression of aerobic and anaerobic glycolysis, inhibition of mitotic activity, and inactivation of some enzyme systems. Small doses of nitrogen mustard produce mutations in the chromosomes of *Drosophila melanogaster* which are similar to those following exposure to x-ray and ultraviolet radiation.[10] In sublethal doses in animals the lymphoid tissues undergo fragmentation and atrophy. The bone marrow suffers depletion of the hematopoietic cells, and the mucosa of the gastrointestinal tract undergoes necrosis and desquamation.

In therapeutic doses in man, the toxic effects include nausea and vomiting several hours after injection, and occasionally diarrhea. Depression of the hematopoietic system with lymphopenia and neutropenia is consistently observed during the first two weeks after treatment. With relatively large doses thrombocytopenia and anemia may also be produced. Subcutaneous infiltration with nitrogen mustard produces a severe local reaction, ranging from edema to slough. Thrombophlebitis at the site of intravenous injection occurs even with the greatest precautions.

Methods

Since large numbers of patients with lymphomas and other neoplastic diseases are observed at the Walter Reed General Hospital, a program was established early in 1946 for the therapeutic application of nitrogen mustard in selected cases.* The diagnosis in every instance was established by biopsy specimens which were reviewed by the Chief of the Pathology Service at Walter Reed Hospital, as well as by the Staff of the Army Institute of Pathology. In some patients additional biopsies were taken during the period of maximum change in size of the lymph nodes. The results of the pathological study of this material will be reported at a later date.

The study of each patient included, in addition to the history and physical examination, measurement of the enlarged lymph nodes, x-ray examinations of the involved systems, complete blood counts, platelet and reticulocyte counts, determination of bleeding, clotting and prothrombin time, sedimentation rate, icteric index, bilirubin, nitrogen, calcium, phosphorus, total and fractional proteins and alkaline phosphatase levels in the blood.

Only one compound, methyl bis beta-chloroethylamine hydrochloride (hereafter referred to as HN_2), was used in all cases. This was obtained in crystalline form, in ampoules containing 10 mg. each, through the Committee on Growth of the National Research Council. The dosage schedule initially was 0.1 mg. per kilogram of body weight per day, repeated on four

* The authors would like to express their gratitude to Dr. Worth B. Daniels, formerly Colonel, M.C., A.U.S., for his important rôle in the initiation of this program, and to Colonel Charles R. Mueller, Chief of the Medical Service, for his encouragement and support in the continuation of this work.

successive days. During the latter part of the study, the dosage was varied to include up to 0.36 mg. per kilo, but the total dose for one course of treatment in any patient did not exceed 46 mg. with the exception of one patient who received 60 mg. The choice of the larger daily doses of HN_2 depended on the general status of the patient, the level of the white blood count and the extent of the disease. Furthermore, in those instances where previous therapy had demonstrated a good tolerance for the drug, with little or no depression in the blood counts, it was considered safe to use more than 0.1 mg. per kilo per day, in an attempt to obtain more effective results. If nausea and vomiting were too distressing, the intervals between the individual injections were extended to 48 hours. The material in each ampoule was dissolved in 10 c.c. of normal saline, producing a concentration of 1 mg. per c.c., and the calculated dose was withdrawn into a 10 c.c. syringe. The needle was then replaced by another dry one, of No. 22 gauge, in order to avoid introduction of the material into the skin and subcutaneous tissues. The injection was made into the largest available antecubital vein and, after it was completed, blood was drawn back and forth into the syringe in an attempt to dilute further any HN_2 remaining in the needle or at the injection site. With this technic, the incidence of thrombophlebitis and subcutaneous reaction was kept at a minimum. In some patients an intravenous infusion of normal saline was started, and the HN_2 solution was injected into the lumen of the rubber tubing or through the air vent. This method gave greater assurance that there was no leakage around the needle, and there were fewer local reactions. The development of nausea and vomiting, which usually occurred between one and three hours after injection, was variable and unpredictable in occurrence and intensity from one patient to another, and often in the same patient during different courses of treatment. Subcutaneous or intramuscular injection of sodium amytal (3.75 to 7.5 grains) was found to be the most effective means of reducing nausea. The administration of atropine or large doses of pyridoxine occasionally afforded the patients some relief. Benadryl was ineffective in combating the gastrointestinal symptoms.

Results

The effects of treatment with HN_2 in each patient were observed with respect to decrease in size of enlarged lymph nodes and visceral masses, subsidence of fever, and improvement in general well being, including increase in appetite, weight and strength. The alterations in blood findings were carefully recorded in order to observe the extent and duration of maximum toxicity of the drug upon the hematopoietic system. The periods of observation varied from two months to one and a half years after treatment.

An attempt was also made to compare the effects of HN_2 with those of roentgen therapy.* This was difficult to ascertain with any degree of ac-

*With the coöperation of Dr. Milton Friedman, former Lt. Col. A.U.S., and Chief, Radiotherapy Section, Walter Reed General Hospital.

TABLE I

Clinical Synopsis of 52 Cases Treated with Nitrogen Mustard
Hodgkin's Disease

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_3 Therapy Begun, Dose	WBC Before Therapy	Post-HN_3 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
No. 1 21 yr. M Nov. 1946	Cervical	Apr. 9 1947 40 mg.	9,750	3,400 6th day 3 days 68%	600,000	10–20%	6 wks., adenopathy	Cervical	Minimal shrinkage in local peripheral adenopathy after HN_3. Remission after x-ray therapy lasting 1½ years.
No. 2 36 yr. M Jan. 1946	Cervical Axillary	June 25, 1946 26 mg.	10,000	5,600 — — 80%	—	80%	3 wks., adenopathy	None	Almost complete shrinkage of peripheral disease after three courses of HN_2 at frequent intervals. Recurrence April 1947. Treated with roentgen therapy.
	As above	July 25, 1946 26 mg.	6,600	4,200 10th day 4 days 61%	—	85%	9 wks., adenopathy	None	
	Cervical	Oct. 30, 1946 26 mg.	9,800	6,050 14th day — 72%	240,000	90%	14 wks., adenopathy	Cervical axillary	
No. 3 19 yr. M Feb. 1946	Cervical	May 17, 1946 27.2 mg.	8,300	4,600 20th day 7 days 63%	85,000	85%	8 wks., adenopathy	None	Complete shrinkage of local lymph nodes obtained after three courses of HN_3 therapy. Recurrence in May 1947 treated with roentgen therapy.
	As above	Aug. 5, 1946 26.4 mg.	7,000	4,500 15th day 10 days 79%	—	90%	8 wks., adenopathy	None	
	As above	Oct. 7, 1946 25.6 mg.	11,000	1,250 15th day 7 days 74%	90,000	95%	16 wks., adenopathy	Cervical	

TABLE I—*Continued*

No. 4 20 yr. M Jan. 1946	Cervical	Nov. 22, 1946 30 mg.	10,000	3,850 11th day 7 days 53%	950,000	60%	3 wks., adenopathy	None	Remission in symptoms but early recurrence of enlarged nodes in area of repeated biopsies which may have impaired the circulation and penetration of HN_2. Nodes regressed completely after radiation therapy. Occult febrile relapse after one year, but no local recurrence.
	As above	Jan. 5, 1947 28.8 mg.	8,300	4,100 6th day 3 days 77%	430,000	65%	—	Left cervical region	
No. 5 18 yr. M 1942	Cervical	Sept. 26, 1946 28.5 mg.	8,800	3,800 21st day 14 days 58%	250,000	50%	5 wks., adenopathy	None	Incomplete shrinkage after HN_2 therapy in long standing disease, with early recurrence. Effective regression of nodes with radiation. No recurrence up to 14 months after x-ray therapy.
	As above	Nov. 14, 1946 28.5 mg.	6,550	3,300 16th day 30 days 73%	280,000	65%	—	Cervical region	
No. 6 29 yr. M June 1945	Retro-peritoneal	June 10, 1946 27.2 mg.	5,700	2,800 18th day 14 days 71%	256,000	95%	6 mos., fever, abdominal mass	None	Excellent remissions following first two courses of HN_2 for extensive retroperitoneal disease. Diminished response after third course. Residual left hydronephrosis. Intensive roentgen therapy (2000 r.×4 in 21 days) produced complete shrinkage of abdominal mass. No recurrence up to 10 months. (See figures 1 and 2.)
		Jan. 11, 1947 27.2 mg.	5,100	2,600 9 days persistent 69%	975,000	80%	2 mos., fever, abdominal mass	None	
		Apr. 8, 1947 30 mg.	4,800	2,750 11th day persistent 90%	300,000	50%	6 wks., fever, abdominal mass	Abdomen	
No. 7 24 yr. M 1942	Cervical	May 28, 1946 22.6 mg.	12,200	3,350 14th day 7 days 52%	82,000	95%	10 mos., fever, adenopathy	None	Complete symptomatic remission in constitutional symptoms and adenopathy over 18-month period with two courses of HN_2.
	As above	July 29, 1947 30 mg.	13,000	4,300 8th day — 69%	200,000	70%	None to 9 mos.	None	

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_3 Therapy Begun, Dose	WBC Before Therapy	Post-HN_3 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
No. 8 29 yr. M May 1945 X-ray to peripheral nodes	Peripheral (Associated hepatitis)	June 14, 1946 22.8 mg.	9,550	3,500 12th day persistent 79%	—	50%	No significant remission	None	Hodgkin's disease complicated by jaundice. Some decrease in jaundice after each of two courses of HN_3 therapy. Biopsy of liver showed "cholangiolitic hepatitis." Lumbar vertebral lesion developed several weeks after concluding HN_3 therapy, and responded to intensive x-ray therapy. Relapse Feb. 1948 with pulmonary and osseous lesions.
	As above	July 26, 1946 22.4 mg.	4,550	3,400 12th day persistent 59%	—	50–70%	No significant remission	None	
No. 9 19 yr. M May 1946	Cervical Axillary Mediastinal	June 25, 1946 32 mg.	7,000	3,600 12th day 8 days 82%	—	85%	4 mos., fever, adenopathy	None	Prompt reduction in adenopathy after first two courses of HN_2. Febrile recurrences responded well to successive courses of HN_2 during 2 year period. (See figures 3, 4, 5.)
	Axillary	Nov. 12, 1946 32 mg.	6,700	3,000 10th day 7 days 89%	210,000	95%	5 mos., fever	None	
	"Occult" febrile	May 8, 1947 30 mg.	6,400	3,150 13th day 12 days 80%	670,000	?	3½ mos., fever	None	
	"Occult" febrile	Sept. 20, 1947 40 mg.	7,100	4,700 6th day 5 days 82%	520,000	?	4 mos., fever, hilar adenopathy	None	

TABLE I—*Continued*

No. 10 24 yr. M Apr. 1946	Axillary Cervical Mediastinal	June 5, 1946 26 mg.	15,150	3,900 10th day 2 days 65%	340,000	Axillary 50%; Cervical 80%; Mediastinal 95%	3 wks., axillary and cervical adenopathy	None	Complete shrinkage of mediastinal and peripheral lymph nodes after two courses of HN_2 therapy, but rapid recurrence in certain areas required roentgen therapy. Third recurrence in retroperitoneal area responded well to HN_2 therapy. (See figures 6, 7, 8.)
	Axillary	July 8, 1946 26.4 mg.	10,150	5,600 10th day 1 day 66%	—	Axillary 80%;	5 wks., adenopathy	Axilla Lower abdomen	
	Mediastinal Retroperitoneal Spleen	Sept. 30, 1947 30 mg.	13,170	4,100 7th day 3 days 70%	325,000	Retroperitoneal 60%; Mediastinal 10%; Spleen 40%	3 mos., fever	Mediastinum	
No. 11 33 yr. M May 1945	Mediastinal Cervical Axillary	May 16, 1946 24.4 mg.	11,750	4,650 7th day 4 days 69%	—	Cervical 40%; Axillary 40%; Mediastinal 10%	3 wks., adenopathy	None	Proved fibrotic type of Hodgkin's disease of more than one year's duration with no response to two courses of HN_2. Intensive x-ray therapy produced complete shrinkage of mediastinal nodes and mild pulmonary fibrosis. (See figures 9, 10, 11, 12.)
	Mediastinal	June 14, 1946 24.4 mg.	17,400	3,600 10th day 10 days 68%	—	None	No remission	Mediastinum	
No. 12 29 yr. M May 1946	Cervical Axillary Mediastinal	June 25, 1946 26.4 mg.	10,600	5,800 8th day — 71%	—	Mediastinal 20%; Cervical and axillary 40–80%	3 wks., adenopathy	None	Moderate shrinkage of peripheral nodes and slight shrinkage in fibrotic mediastinal nodes. Mediastinal recurrence two weeks after second course of NH_2 therapy. Lesion responded satisfactorily to radiation therapy.

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_2 Therapy Begun, Dose	WBC Before Therapy	Post-HN_2 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
	As above	July 22, 1946 26.4 mg.	9,200	4,800 6th day — 73%	—	Mediastinal 50%; Cervical and axillary 90%	2 wks., adenopathy	Mediastinum, axilla	
No. 13 20 yr. M Feb. 1945 X-ray to peripheral nodes	Viscera Retroperitoneal	May 21, 1947 30 mg.	16,600	5,900 13th day — 62%	190,000	Liver and spleen 10%	1 wk., fever	None	Visceral and retroperitoneal involvement with incomplete responses after conventional HN_2 dosage. Marked resistance to HN_2 toxic effects. Symptomatic remission ultimately obtained after persistent intensive therapy and the production of a leukopenia. Osseous lesions developed despite HN_2 therapy, and required roentgen therapy.
	As above	June 9, 1947 30 mg.	15,500	3,300 11th day 2 days 59%	220,000	10–20%	1 wk., fever	None	
	As above	July 1, 1947 46 mg.	12,000	3,800 15th day 5 days 53%	190,000	20–40%	2 wks., fever	None	
	Visceral Osseous	Aug. 5, 1947 46 mg.	6,300	750 13th day 27 days 50–70%	80,000	40–50%	4 wks., fever, enlarging viscera	None	
	As above	Sept. 26, 1947 20 mg.	12,000	7,700 11th day — 85%	260,000	20%	5 wks., fever, osseous lesions	Pelvis	
	As above	Dec. 2, 1947 24.5 mg.	8,400	4,200 17th day 3 days 82%	325,000	20%	2 wks., fever, pain	Knee	

TABLE I—*Continued*

No. 14 29 yr. M Apr. 1946	Cervical Axillary	May 28, 1946 23.6 mg.	12,500	6,150 6th day — 74%	106,000	90%	4 wks., adenopathy	—	Symptomatic remission after each course of HN_2. Roentgen therapy and HN_2 equally effective in reducing lesions, but more rapid recurrence after the latter. Roentgen therapy ineffective for terminal abdominal disease. No significant leukopenia despite persistent HN_2 therapy. Died May 17, 1947.
	As above	Aug. 5, 1946 23.3 mg.	11,900	5,600 10th day — 63%	—	90%	8 wks., adenopathy	Right cervical area	
	Retro-peritoneal	Nov. 19, 1946 22.4 mg.	14,400	8,400 9th day — 82%	—	70%	5 wks., abdominal mass, fever, cachexia		
	As above	Jan. 15, 1947 21.2 mg.	12,800	8,100	110,000	40%	3 wks., as above	—	
	Hepatic Retro-peritoneal	Feb. 24, 1947 20 mg.	14,200	6,250 7th day — 94%	180,000	30%	2 wks., as above	—	
	As above	Mar. 4, 1947 20 mg.	11,600	6,000 10th day — 92%	165,000	20%	2 wks., as above	Abdomen	
No. 15 30 yr. M May 1946	Cervical Inguinal	Oct. 7, 1946 19 mg.	9,600	2,600 17th day persistent 60%	—	Cervical 75%; Inguinal; 50%	3 wks., fever, adenopathy	None	Marked symptomatic improvement with weight gain and shrinkage of nodes. Rapid febrile recurrences were associated with enlargement of lymph nodes. Satisfactory palliation for 5 month period. Terminal cachectic state associated with persistent vomiting and diarrhea and a hepatitis. Died April 14, 1947. (See case history.)
	As above	Nov. 14, 1946 19.8 mg.	5,100	1,200 19th day 21 days 55%	260,000	Cervical 95%; Inguinal 60%	3 wks., as above	None	
	Inguinal Periaortic	Dec. 13, 1946 23.2 mg.	6,800	1,750 17th day persistent 74%	184,000	70%	3 wks., as above	None	

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_3 Therapy Begun, Dose	WBC Before Therapy	Post-HN_3 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
	Periaortic Visceral	Jan. 25, 1947 18.6 mg.	5,900	1,350 14th day persistent 81%	156,000	?	1–2 wks., as above	None	
	As above	Feb. 21, 1947 10 mg.	5,000	1,600 13th day persistent 83%	450,000	?	None	None	
	As above	Mar. 18, 1947 10 mg.	19,250 (enteritis)	2,200 10th day persistent 79%	100,000	?	None	None	
No. 16 32 yr. M Mar. 1945 X-ray to peripheral nodes	Visceral Retroperitoneal	May 16, 1946 24.8 mg.	5,150	3,160 7th day 3 days 68%	230,000	?	4 wks., fever	Liver and spleen	Remission in marked constitutional symptoms of terminal abdominal Hodgkin's disease of the "occult febrile" type. Improvement concomitant with leukopenia to 150 cells per cu. mm. Patient ambulatory for several weeks with leukopenia of 500 cells per cu. mm. Symptomatic improvement sustained on "maintenance" mustard therapy of one injection per week. Terminal hepatitis possibly of homologous serum type, with associated hemorrhagic manifestations. Died February 23, 1947.
	As above	Oct. 29, 1946 9 mg.	3,800	1,550 18th day persistent 35%	96,000	As above	16 days, fever	None	
	As above	Nov. 26–Feb. 10, 1947 30 mg.	2,600	150 — — —	5,000	As above	Febrile remission	None	

TABLE I—*Continued*

No. 17 20 yr. M Mar. 1943 X-ray to mediastinal and peripheral nodes	Peripheral Retro-peritoneal	June 10, 1946 21.4 mg.	7,300	2,500 8th day 6 days 75%	240,000	Peripheral 60%; Retro-peritoneal 40%	3 wks., fever, enlarge-ment of lymph nodes	None	Brief response in abdominal Hodgkin's disease of long stand-ing. No significant improve-ment after x-ray therapy to the abdomen. Died Dec. 12, 1946.
	As above	July 8, 1946 10.8 mg.	7,200	2,300 9th day 7 days 81%	—	Peripheral 85%; Retro-peritoneal 30%	3 wks., as above	Abdomen	
No. 18 34 yr. Apr. 1946	Generalized, Peripheral	May 2, 1946 21.6 mg.	5,300	2,300 7th day persistent 73%	121,000	Peripheral 30%; Parasternal 100%; Paraverte-bral, 10%	3 wks., fever	Paraverte-bral region	Temporary remission with shrinkage of peripheral nodes, but no effect on fibrosing infil-trative Hodgkin's disease in-volving vertebrae. Died Dec. 29, 1946.
No. 19 26 yr. M 1944 X-ray to mediastinal and peripheral lymph nodes	Generalized	June 13, 1947 30 mg.	3,200	900 11th day persistent 67%	170,000	None	2 wks., fever	None	Terminal leukopenia sclerosing Hodgkin's disease with slight symptomatic remission after HN_2 therapy. Died Sept. 4, 1947.
No. 20 24 yr. M June 1947	Generalized (febrile) (fulminat-ing)	Aug. 18, 1947 30 mg.	2,900	2,000 10th day persistent 84%	160,000	Peripheral nodes 30%	None	None	Fulminating visceral and periph-eral necrotizing disease not re-sponding to adequate HN_2 therapy despite marked shrink-age of involved organs. Died Sept. 22, 1947.
	As above	Sept. 6, 1947 40 mg.	2,150	500 12th day persistent 80–90%	11,000	Peripheral nodes 70%	None	None	

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_3 Therapy Begun, Dose	WBC Before Therapy	Post-HN_3 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
No. 21 28 yr. M June 1945	Peripheral Retro-peritoneal Visceral	May 2, 1946 20.4 mg.	3,600	2,250 5th day persistent 81%	134,000	None	None	Liver and spleen	Terminal leukopenic Hodgkin's disease with no significant improvement from HN_3 or radiation therapy. Died Nov. 4, 1946.
	As above	June 3, 1946 19.6 mg.	4,500	1,200 8th day persistent 64%	190,000	Peripheral nodes 40%	None	None	
No. 22 29 yr. M Nov. 1945 X-ray to mediastinum and vertebrae	Generalized	July 4, 1946 28 mg.	6,300	3,750 11th day 6 days 66%	—	Peripheral nodes 10–20%	3 wks., fever and adenopathy	Abdomen	Brief response in terminal generalized Hodgkin's disease in which further x-ray therapy did not alter the clinical course. Exfoliative dermatitis occurred two weeks after HN_3 therapy. Died Oct. 4, 1946, with coexistent tuberculosis and Hodgkin's disease.
No. 23 22 yr. M Apr. 1947 X-ray to cervical lymph nodes and pelvis	Osseous Retro-peritoneal	Jan. 6 1948 20 mg.	14,500	4,200 16th day 4 days 81%	700,000	?	5 wks., fever, osseous pain	None	Temporary febrile remission, indisseminated Hodgkin's disease, but no satisfactory relief from pain produced by osseous lesions.
No. 24 29 yr. M Dec. 1943 X-ray to peripheral lymph nodes	"Occult" febrile	Nov. 12, 1946 26 mg.	5,800	2,450 7th day 7 days 71%	—	?	2 mos., fever	None	Symptomatic remission in a chronic case of "occult" febrile Hodgkin's disease after each course of HN_3.

TABLE I—*Continued*

	As above	May 8, 1947 30 mg.	4,600	2,000 6th day persistent 76%	400,000	?	2½ mos., fever	Abdomen	
	As above	Dec. 11, 1947 10 mg.	4,750	3,150 6th day persistent 77%	308,000	?	6 wks., fever	None	
No. 25 35 yr. M Jan. 1945 X-ray to vertebrae	"Occult" febrile	Aug. 9, 1947 40 mg.	7,250	4,000 6th day 4 days 82%	650,000	?	5 mos., fever	None	Excellent remission from symptoms of occult febrile Hodgkin's disease.
No. 26 23 yr. M Dec. 1946 X-ray to mediastinum and peripheral lymph nodes	"Occult" febrile (Panhematopenia)	Aug. 6, 1947 40 mg.	4,050	1,500 6th day 30 days 76%	9,800	?	None up to 7 mos.	None	Persistent severe panhematopenia in disseminated Hodgkin's disease for several months before and after roentgen therapy administered February 1947. Febrile relapse and panhematopenia responded to HN_2 therapy with dramatic results and a return to normal in the clinical, blood, and bone marrow findings.
No. 27 22 yr. M Mar. 1945 X-ray to peripheral and mediastinal lymph nodes	"Occult" febrile	May 2, 1946 20 mg.	2,200	1,350 12th day persistent 75%	14,360	?	3 wks., fever	None	Temporary remission in terminal leukopenic phase of generalized Hodgkin's disease previously treated by roentgen therapy. HN_2 given with leukopenia of 2,000 and remission induced with counts as low as 900 per cu. mm. Ultimate thrombopenia with diffuse hemorrhagic manifestations. Died July 8, 1946.
	As above	July 1, 1946 18 mg.	2,500	950 7th day continuous 65%	12,200	?	None	None	

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_2 Therapy Begun, Dose	WBC Before Therapy	Post-HN_2 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
Lymphomas Other Than Hodgkin's Disease									
No. 28 24 yr. F Lymphosarcoma Apr. 1947	Generalized (x-ray to tonsils, lymph nodes)	July 3, 1947 30 mg.	3,500	650 8th day persistent 65%	65,000	Peripheral lymph nodes and mediastinum 10–20%	No remission	Mediastinum and lungs	Fulminating generalized lymphosarcoma with no clinical or symptomatic remission, but slight shrinkage of lymph nodes. Died July 22, 1947.
No. 29 24 yr. M Lymphosarcoma Oct. 1946	Generalized and subcutaneous (x-ray to lymph nodes, kidneys, mediastinum)	July 14, 1947 20 mg.	2,700	1,500 4th day persistent 69%	285,000	20–90% Av.–75%	3 wks., re-growth of subcutaneous metastases	100 to 300 r. to subcutaneous lesions	Prompt response to HN_2 therapy in numerous subcutaneous lesions shown to be sensitive to 100 to 200 r. of roentgen therapy. Satisfactory temporary clinical remissions were associated with shrinkage of the lesions. Died Dec. 9, 1947.
	As above	Aug. 26, 1947 30 mg.	4,700	1,650 13th day persistent 66%	250,000	10–90% Av.–50%	5 wks., recurrent infiltrations	None	
No. 30 18 yr. M Reticulum cell sarcoma July 1946	Generalized and subcutaneous (x-ray to mediastinum)	Mar. 5, 1947 30 mg.	3,900	2,000 15th day persistent 75%	90,000	90%	10 days Recurrent infiltrations	None	Four successive brief remissions with prompt shrinkage of lymph nodes and subcutaneous nodule, in a proved x-ray-sensitive reticulum cell sarcoma. Persistent severe leukopenia during treatment. Sharp rise in white count despite intensive HN_2 therapy prior to death. Died May 22, 1947.
	As above	Mar. 27, 1947 20 mg.	2,600	2,400 8th day persistent 68%	63,000	80%	10 days As above	None	

TABLE I—*Continued*

	As above	Apr. 15, 1947 20 mg.	3,500	2,200 8th day persistent 77%	28,000	60%	10 days As above	None	
	As above	May 2, 1947 20 mg.	3,300	1,400 10th day 18 days 89%	22,000	50%	10 days As above	None	
No. 31 31 yr. M Reticulum cell sarcoma 1945	Generalized (x-ray to mediastinum, abdomen)	May 10, 1947 20 mg.	3,800	150 — — 60%	28,000	None	No remission	None	No effect on extensive terminal reticulum cell sarcoma infiltrating the viscera and the osseous system. Marked leukopenia but no hemorrhagic manifestations prior to death. Died May 23, 1947.
No. 32 18 yr. M Reticulum cell sarcoma May 1946	Generalized	June 8, 1946 22 mg.	20,100	4,800 9th day 2 days 87%	—	None	No remission	None	No alteration in course of disease. Poor response to fractional x-ray therapy to the abdomen simultaneously with fractional HN_2 therapy. Died Nov. 23, 1946.
	As above	June 28–July 15 21 mg. (with x-ray)	10,250	3,750–32nd day persistent 71%	—	None	No remission	Abdomen	
No. 33 68 yr. F Reticulum cell sarcoma Jan. 1946	Generalized	July 25, 1946 24 mg. (with x-ray)	3,500	1,900 9th day persistent 73%	—	None	No remission	Chest and abdomen	Terminal disseminated reticulum cell sarcoma not responsive to combined HN_2 and x-ray therapy. Died September 1, 1946.
No. 34 21 yr. M Reticulum cell sarcoma Nov. 1945	Generalized (x-ray to mediastinum)	June 13, 1946 24.8 mg	12,000	3,600 9th day — 73%	—	None	No remission	None	No response to HN_2 therapy in terminal disseminated disease previously shown to be moderately resistant to x-ray therapy. Died June 28, 1946.

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_2 Therapy Begun, Dose	WBC Before Therapy	Post-HN_2 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
No. 35 22 yr. M Reticulum cell sarcoma June 1947	Naso-pharynx Cervical Spleen	Oct. 1, 1947 30 mg.	25,700	4,200 20th day 6 days 79%	696,000	Left cervical 95%; spleen 20–40%	6 wks., periosteal lesions	Osseous	Immediate symptomatic remission in fever and splenomegaly. Marked shrinkage of left cervical lymph nodes in reticulum cell sarcoma shown to be x-ray sensitive in the right cervical and nasopharyngeal region. Six weeks later relapse in distant organs treated with roentgen therapy.
No. 36 61 yr. M Chronic lymphatic leukemia 1944	Generalized	July 31, 1946 26 mg.	141,000	26,900 28th day — —	65,000	Lymph nodes 20%	No remission	Spleen	No clinical improvement in chronic lymphatic leukemia despite fall in peripheral WBC's. Exfoliative dermatitis occurred six weeks after HN_2 therapy. Died July 14, 1947.
No. 37 19 yr. M Subacute myelogenous leukemia (myelosarcoma) July 1946	Generalized	Jan. 16, 1947 21.6 mg.	3,000	2,200 — — —	27,200	Lymph nodes 50%	1 wk., fever toxemia	None	Marked shrinkage in lymph nodes with disappearance of superior vena caval obstruction, and slight symptomatic remission. Autopsy revealed massive necrosis of infiltrated lymph nodes. Died January 27, 1947.
No. 38 21 yr. M Subacute myelogenous leukemia July 1946	Generalized Cutaneous	May 30, 1947 20 mg.	75,000	6,400 6th wk. — 92%	28,000	Skin 50%; spleen 10%	6 wks., increasing WBC	Spleen	Symptomatic remission and marked shrinkage of extensive leukemia cutis after single course of HN_2, but little improvement in visceropathy or anemia. Died September 16, 1947.

TABLE I—*Continued*

No. 39 Lympho-leukosarcoma (Sternberg) Apr. 1946	Generalized	Mar. 6, 1947 23.2 mg.	31,000	3,400 18th day — —	370,000	Lymph nodes 90%	7 mos., fever adenopathy	Peripheral lymph nodes	Marked symptomatic improvement associated with satisfactory fall and shrinkage in lymph nodes. Recurrence October 1947 after seven months of total clinical remission.
No. 40 40 yr. M Lympho-leukosarcoma (Sternberg) May 1946	Generalized (x-ray to tonsil and neck)	June 30, 1947 30 mg.	4,250	2,800 8th day persistent 67%	—	20–50%	5 wks., adenopathy and tonsillar enlargement	None	Clinical remission after first course of HN_2 but subsequent failure to respond in moderately x-ray resistant lympholeukosarcoma. Died September 27, 1947.
	As above	Aug. 20, 1947 40 mg.	5,500	3,800 6th day persistent 27%	60,000	None	No remission	Tonsil Peripheral lymph nodes	
	As above	Sept. 15, 1947 26.4 mg.	14,100	3,150 8th day 6 days 11%	12,800	None	—	None	
No. 41 36 yr. M Giant follicular lympho-blastoma Jan. 1946	Cervical Axillary	May 28, 1946 28.4 mg.	11,000	4,000 8th day 3 days 79%	372,000	95%	None up to 9 mos.	None	Excellent prolonged clinical remission with almost total obliteration of involved tissue.
No. 42 25 yr. M Giant follicular lympho-blastoma Apr. 1946	Axillary Cervical	June 25, 1946 26 mg.	12,950	5,100 7th day — 81%	—	75%	3 wks., adenopathy	None	Effective reduction in lymph nodes with symptomatic remission for more than 14 months after three courses of HN_2 therapy.

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_2 Therapy Begun, Dose	WBC Before Therapy	Post-HN_2 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
	Axillary	Aug. 26, 1946 26 mg.	10,200	5,750 9th day — 75%	—	85%	8 wks., adenopathy	None	
	Cervical	Nov. 5, 1946 26 mg.	9,200	8,150 9th day — 82%	125,000	95%	None up to 14 mos.	None	
No. 43 38 yr. M Giant follicular lymphoblastoma 1942	Generalized	Oct. 27, 1947 30 mg.	7,000	3,100 11th day 8 days 72%	666,000	Spleen 50%; Peripheral 90%	None up to 4 mos.	Inguinal region for obstructive adenopathy	Marked symptomatic remission and shrinkage of spleen and peripheral lymph nodes in proved roentgensensitive lymphoma.
No. 44 23 yr. M Boeck's sarcoid 1943	Pulmonary Peripheral	Nov. 12, 1946 28 mg.	5,650	3,600 6th day 20 days 60%	267,000	None	—	None	No response to HN_2 therapy.
				Miscellaneous Malignant Diseases					
No. 45 37 yr. M Bronchogenic carcinoma Dec. 1945	Cervical Mediastinal Pulmonary	May 2, 1946 22.4 mg.	5,900	3,150 15th day 10 days 57%	120,000	20%	1 wk., adenopathy pleural fluid	Pulmonary (with HN_2)	Temporary symptomatic improvement and absorption of pleural fluid with some shrinkage of nodes. New metastatic lesions developed and progressed 3 weeks after therapy was completed. Died August 31, 1946.
	As above	June 13, 1946 (with x-ray) 22.4 mg.	5,100	2,000 12th day 21 days 64%	—	0–40%	No remission	None	

TABLE I—*Continued*

No. 46 40 yr. M Adeno-carcinoma of lung Sept. 1946	Pulmonary Peripheral Lymph nodes	July 9, 1947 30 mg.	11,000	4,500 12th day 2 days 80%	600,000	None	No remission	None	No shrinkage of adenocarcinomatous metastases, but slight improvement in cough, dyspnea, and well being. Died September 29, 1947.
	As above	Aug. 19, 1947 20 mg.	6,750	3,550 16th day 5 days 67%	600,000	None	As above	None	
	Subcutaneous As above	Sept. 19, 1947 20 mg.	12,900	4,300 — — 74%	512,000	None	As above	None	
No. 47 28 yr. M Seminoma of testis Mar. 1945	Pulmonary Retro-peritoneal	Feb. 6, 1947 40 mg.	14,000	8,000 7th day — 94%	440,000	Epigastric mass 40%	2 wks., adenopathy	None	Dramatic brief remission in moribund patient with extensive retroperitoneal lesions which diminished markedly in size. Lower retroperitoneal lesions were previously responsive to x-ray therapy. Died February 24, 1947.
No. 48 24 yr. M Adeno-carcinoma of testis Nov. 1945	Pulmonary Retro-peritoneal	Mar. 20, 1947 30 mg.	12,000	6,400 8th day — 90%	65,000	None	No remission	None	No response to HN_2 in moderately x-ray resistant adenocarcinoma of testes. Died April 5, 1947.
No. 49 25 yr. M Apr. 1946 Terato-carcinoma of testis	Pulmonary Retro-peritoneal	Oct. 21, 1947 30 mg.	9,300	4,300 11th day 6 days 75%	800,000	None	No remission	Lung	Multiple pulmonary metastases not responding to two courses of HN_2 therapy. Shrinkage of tumor areas occurred only in locally irradiated masses. Died December 21, 1947.

TABLE I—*Continued*

Patient, Age, Onset Prior Therapy	Region Involved	Date HN_3 Therapy Begun, Dose	WBC Before Therapy	Post-HN_3 Leukopenia, Day of Occurrence, Duration, Per Cent Neutrophiles	Lowest Platelet Count After Therapy	Maximum Total Lymph Node Shrinkage	Recurrence Interval Type	Subsequent X-ray Therapy	Remarks
	As above	Nov. 26, 1947 30 mg.	7,200	2,500 12th day persistent 84%	1,000,000	None	No remission	None	
No. 50 46 yr. M Transitional cell carcinoma Feb. 1946	Nasopharynx Cervical Hepatic	Nov. 12, 1946 25.4 mg.	12,000	4,800 10th day 1 day 76%	170,000	Nasopharynx and cervical—50%	2½ wks., adenopathy	None	Marked shrinkage of primary lesions and regional metastases with relief of obstructive symptoms. Liver metastases and clinical course unaffected. Died January 2, 1947.
	As above	Dec. 2, 1946 24.8 mg.	5,600	6,900 17th day — 77%	211,000	Nasopharynx and cervical—60%	No significant remission	None	
No. 51 22 yr. M Metastatic carcinoma Feb. 1945	Cervical (x-ray to right neck)	Dec. 6, 1946 28 mg.	6,700	3,700 13th day 9 days 75%	300,000	None in site of previous x-ray; 20% elsewhere	No remission	Cervical	Recent metastatic lymph nodes showed slight shrinkage but no response was observed in sites of previous x-ray therapy. Died March 30, 1947.
No. 52 34 yr. M Metastatic sarcoma (neurogenic?) Nov. 1945	Generalized	Mar. 24, 1947 30 mg.	12,700	3,420 — — 68%	52,000	None	—	None	No effect on diffuse sarcoma (neurogenic, chrondrous, or anaplastic). Died April 7, 1947.

curacy. Certain patients with multiple lesions were given x-ray irradiation over local areas, and HN_2 therapy at the same time. The rate of recurrence in the areas not treated with x-ray was compared with those which had been irradiated. Other patients were given HN_2, and after the length of time for recurrence of enlarged lymph nodes was ascertained, they were treated

FIG. 1. *Case 6.* Pronounced enlargement of retroperitoneal lymph nodes due to Hodgkin's disease, with deviation of left ureter as seen by retrograde pyelogram. Right ureter not visualized.

with roentgen radiation and the period of remission again observed. Finally, patients who had been treated with x-ray were subsequently given HN_2 and the results compared.

The observations on all the patients treated are summarized in table 1.

HODGKIN'S DISEASE

Twenty-seven patients with Hodgkin's disease were treated in this series. Most of these had not been treated previously with x-ray. For purposes

of description, the cases have been divided into three groups with respect to the most prominent manifestations of the disease.

1. Focal Lymph Node Enlargement and Minimal Constitutional Symptoms. In this group are included 12 patients with single or multiple areas of involvement in the peripheral, mediastinal or retroperitoneal regions, and little, if any, fever, weight loss, anemia or debility. In six individuals with

FIG. 2. *Case 6.* Reduction in retroperitoneal mass following a single course of HN_2, with return of ureters to a more normal position.

a single localized group of enlarged lymph nodes, one (case 1) showed no response, but in the other five pronounced shrinkage was produced with HN_2. Four of these (cases 2 to 5) had recurrence of the enlarged nodes in three to eight weeks, and were treated with intensive roentgen radiation, which produced prolonged remissions. Case 1 also showed a good response to x-ray therapy. In case 6 (figures 1 and 2) a large retroperitoneal mass,

proved by laparotomy to be Hodgkin's disease, regressed almost completely for periods of six, three and two months after successive courses of HN_2. X-ray therapy was finally given to reduce a mild obstructive hydronephrosis which had not yielded completely to HN_2 therapy. A prolonged remission was thereby produced.

Among the other six patients, who had multiple involvement in the peripheral and mediastinal regions two (cases 7 and 8) were adequately

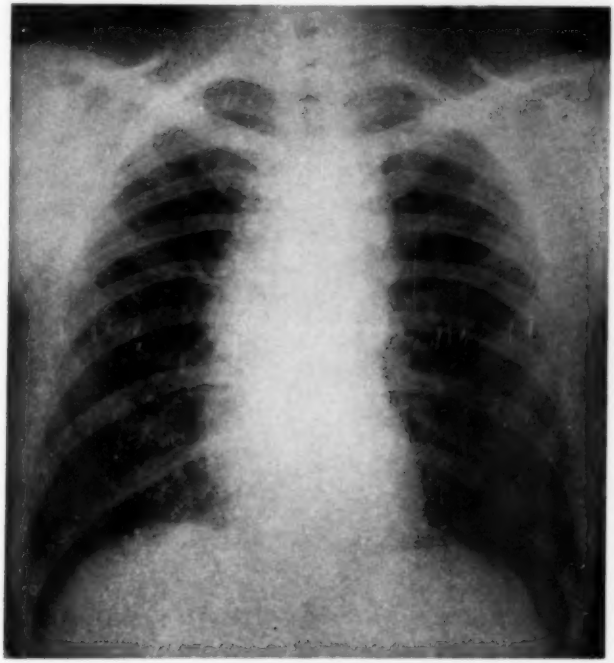

FIG. 3. *Case 9.* Hodgkin's disease. Enlarged mediastinal lymph nodes prior to HN_2 therapy.

controlled by repeated courses of HN_2 alone, while the other four (cases 9 to 12) (figures 3 to 12) showed varying responses in the different areas, and required roentgen irradiation to effect prolonged regression of the adenopathy. In one instance (case 11) the mediastinal nodes, which were refractory to HN_2 were known to be involved by a fibrosing type of Hodgkin's lesion.

From the observations in this group of patients, it was apparent that focal lymph node disease was better controlled by x-ray therapy than by HN_2.

2. Generalized Disease with Pronounced Constitutional Symptoms. The

11 patients in this group had fever, cachexia, anemia, retroperitoneal adenopathy and visceral disease, with only minimal mediastinal and peripheral node involvement. Five of these patients also exhibited a persistent leukopenia prior to HN_2 therapy, and all of them were considered to be in the terminal phase of the disease. Temporary remission in symptoms was obtained in four (cases 13 to 16) for periods of three to six weeks. There

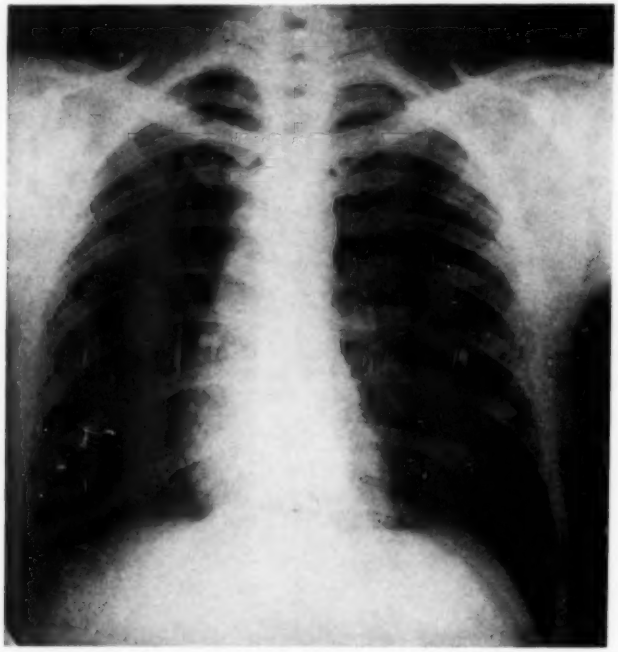

FIG. 4. *Case 9.* Complete shrinkage of hilar lymphadenopathy after one course of HN_2.

was noted a dramatic improvement in fever, weight, appetite and well-being in association with shrinkage of the enlarged nodes (see figure 13 for illustrative case 15). In the other seven patients (Nos. 17 to 23) little, if any, significant response was noted. In one instance (case 18) the lack of effect was due possibly to the fibrosing character of the lesions, and in another (case 20) it may have been related to the extensive necrotizing nature of the disease. The reason for the failure of the others to respond favorably was not evident. In this group, therefore, it would seem that in a fair proportion of the cases some benefit was achieved with HN_2 therapy.

3. "Occult" Febrile Disease. Four patients (Nos. 24 to 27) had persistent or recurrent fever with no clinically demonstrable lymph node or

visceral involvement at the time of treatment with HN_2, although previous lymph node biopsies had proved the presence of Hodgkin's disease. The constitutional symptoms responded promptly to therapy in every case. Two patients (Nos. 24 and 25) were maintained in a state of well-being for periods of five and 13 months, respectively, one with a single course, the other with three courses of HN_2. A remarkable response was obtained in patient 26.

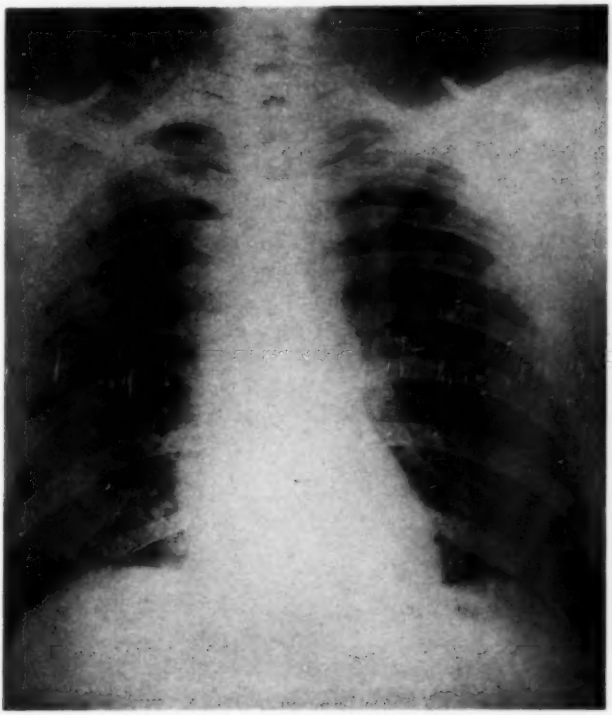

FIG. 5. *Case 9.* Recurrence of mediastinal adenopathy 18 months after HN_2 therapy was begun. A total of four courses of treatment (total dose 134 mg.) was given during this interval.

He showed a persistent severe pancytopenia from two months before, to five months after roentgen therapy had been administered to the mediastinum and peripheral nodes. He developed purpura, marked anemia, a hypoplastic bone marrow, weakness and high fever, which seemed to indicate the onset of the terminal stage. One course of HN_2 was followed by prompt subsidence of fever, return of strength and well-being, and improvement in the blood and bone marrow state to normal. This patient has remained apparently well for 30 months of observation. The fourth patient (No.

27), who was moribund at the time of treatment, responded with a brief remission. This group showed the most consistent and dramatic responses to HN_2 therapy.

Lymphosarcoma

Two patients with this disease were treated with nitrogen mustard. One (No. 28) did not respond well to either HN_2 or x-ray therapy. The other (No. 29) had wide-spread lesions in the subcutaneous tissues, as well as in

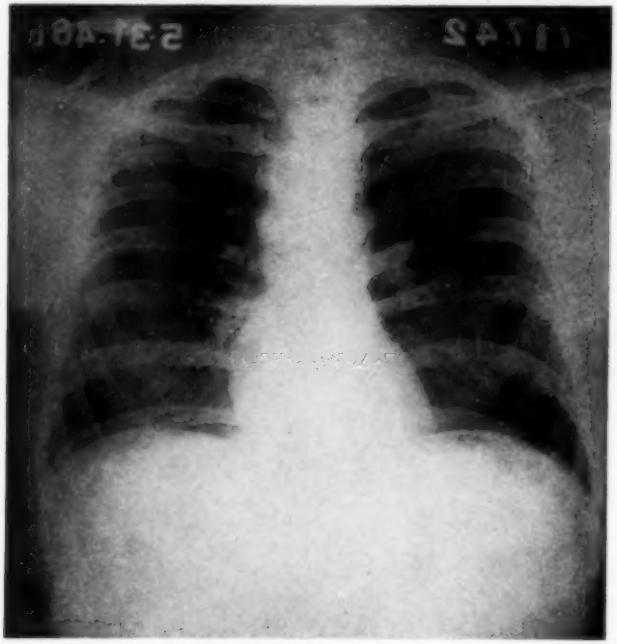

Fig. 6. *Case 10.* Hodgkin's disease. Mediastinal enlargement, prior to treatment with HN_2.

the pericardium and kidneys. The subcutaneous lesions were highly radiosensitive, as was demonstrated when certain ones were treated with 100 to 300 r of x-ray, and disappeared completely. With two courses of HN_2, shrinkage in these lesions varied from 50 per cent to 95 per cent, but they recurred in several weeks.

Reticulum Cell Sarcoma

Of six patients in this group, one (No. 30) had a good though brief response to HN_2, while four (Nos. 31 to 34) showed little effect. They also responded poorly to radiation. The sixth case (No. 35) had a lesion

in the nasopharynx, bilateral cervical masses, fever and splenomegaly. He was given roentgen therapy to the right side of the neck and right nasopharyngeal region, with a total dose of 2000 r over a three week period. It was calculated that less than 5 per cent of this dose penetrated to the left side of the neck. He was also given a course of HN_2 therapy at the beginning of the x-ray treatments. There was an immediate remission in fever and

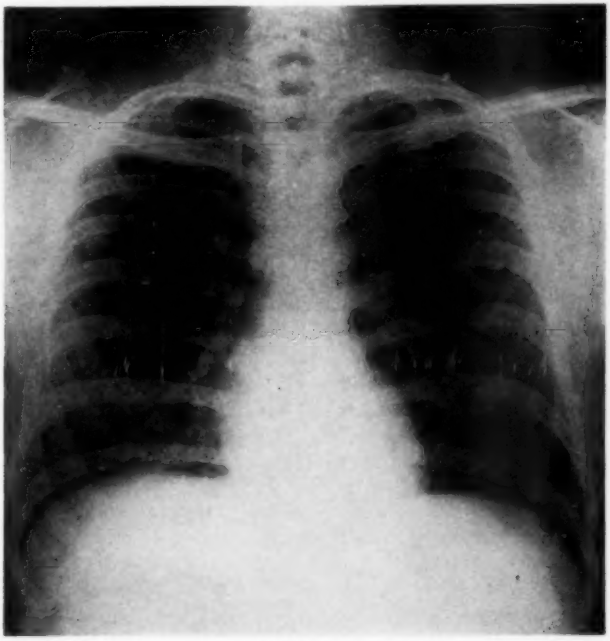

FIG. 7. *Case 10.* Complete regression of hilar lymphadenopathy six weeks after second course of HN_2.

marked shrinkage of the spleen, as well as pronounced decrease in size of the nodes in both sides of the neck. The patient later developed periosteal lesions in the skull and right femur.

LEUKEMIAS

One patient (No. 36) with chronic lymphatic leukemia showed a fall in the peripheral lymphocyte count following nitrogen mustard therapy, but no change in size of the spleen or liver, and no symptomatic improvement.

Two patients (Nos. 37 and 38) with subacute myeloid leukemia, responded with marked shrinkage of lymph nodes in one instance, and exten-

sive skin lesions in the other. There was no apparent alteration in the clinical course of either patient.

Two patients (Nos. 39 and 40) with lympholeukosarcoma (Sternberg) showed remissions for five months and six weeks respectively, in symptoms, blood counts and lymph nodes.

Giant Follicular Lymphoblastoma

In one case (No. 41) of giant follicular lymphoblastoma, a single course of HN_2 produced a rapid and almost complete disappearance of large masses

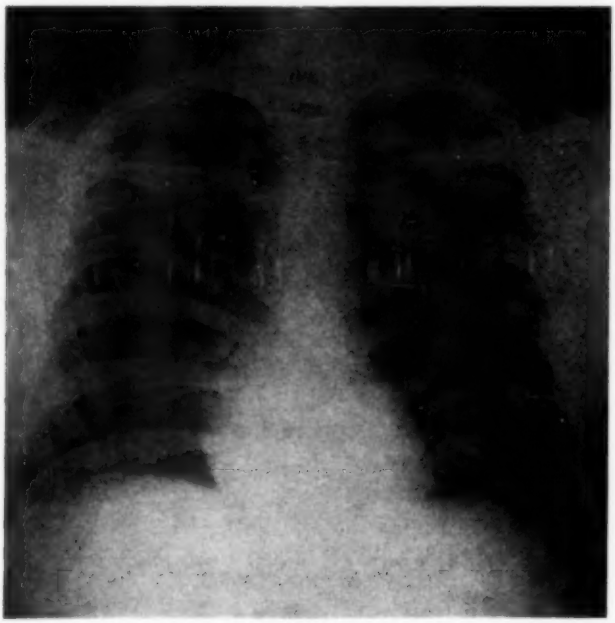

Fig. 8. *Case 10.* Recurrence of mediastinal adenopathy one year after nitrogen mustard therapy.

of lymph nodes. Another patient (No. 42) responded more slowly, but after three courses of treatment became free of adenopathy except for a few small residual nodes. Nine months' follow-up has revealed no recurrence in either patient. A third patient (No. 43) with lymphadenopathy of six years' duration showed a marked remission, with shrinkage of spleen and lymph nodes after a single course of HN_2. This patient was free of detectable disease four months after treatment.

Boeck's Sarcoidosis

One patient (No. 44) with pulmonary and peripheral sarcoid lesions showed no changes after HN_2 therapy.

Bronchogenic Carcinoma

One patient (No. 45) with an undifferentiated carcinoma of the lung, had a large mass in the right thorax with a pleural effusion. The pleural

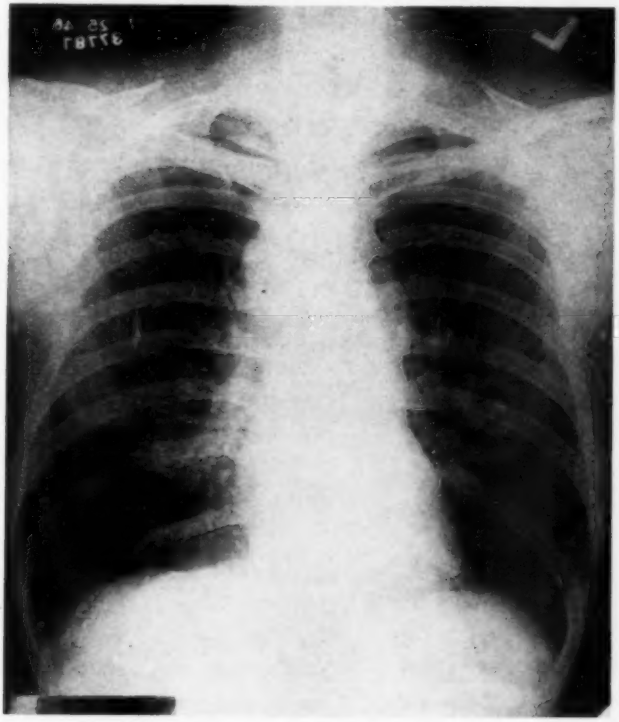

Fig. 9. *Case 11.* First roentgenogram at the time of discovery of mediastinal involvement. No other lymph node enlargement found.

fluid disappeared after HN_2 therapy, and the pulmonary mass decreased about 50 per cent in size. The patient died subsequently of multiple metastases to the brain and other organs. Another patient (No. 46) with an adenocarcinoma of the lung responded with temporary symptomatic improvement in cough, dyspnea and hemoptysis, but no significant shrinkage of peripheral metastases and no alteration in the appearance of the chest x-ray.

Testicular Tumors

One patient (No. 47) with a seminoma, which had previously been responsive to x-ray therapy for two years showed an excellent temporary symptomatic remission and shrinkage of a retroperitoneal mass for about three weeks after HN_2 therapy. Another individual (No. 48) with an embryonal adenocarcinoma of the testis, which had been moderately resistant to x-ray therapy, did not show any response to nitrogen mustard. In an-

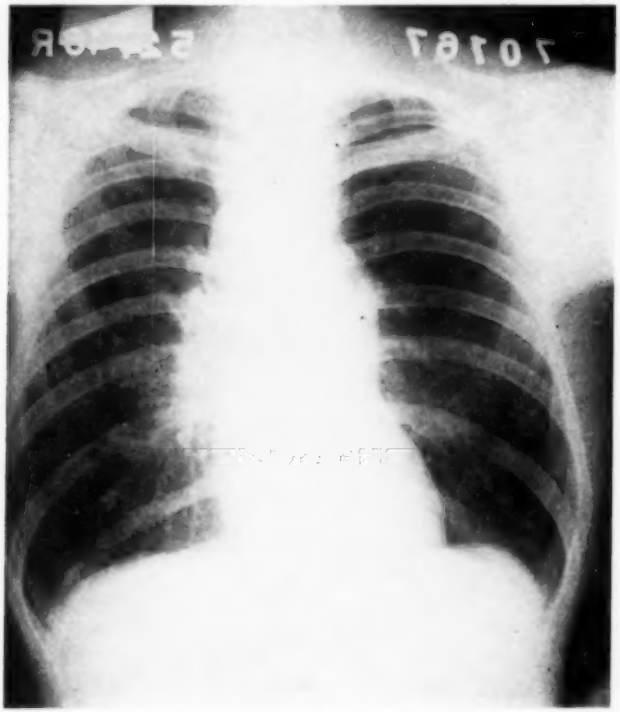

Fig. 10. *Case 11.* X-ray of chest 10 months after preceding film with no therapy revealed no change in hilar mass. Exploratory thoracotomy and biopsy revealed fibrous type of Hodgkin's disease.

other instance (No. 49) a teratocarcinoma, with choriocarcinomatous pulmonary metastases, showed no shrinkage in a recurrent iliac lesion, but some remission in constitutional symptoms referable to the pulmonary metastases.

Transitional Cell Carcinoma

Patient 50 had large cervical masses and numerous liver metastases from a transitional cell carcinoma of the nasopharynx. Following treatment with

HN_2 there was a striking decrease in the size of the primary tumor and of the cervical metastases, but no change in the size of the liver.

Metastatic Carcinoma

One patient (No. 51) with extensive cervical metastatic carcinoma of undetermined origin, showed little improvement after HN_2 therapy. Another (No. 52) with diffuse sarcoma, type undetermined, also showed no response to nitrogen mustard.

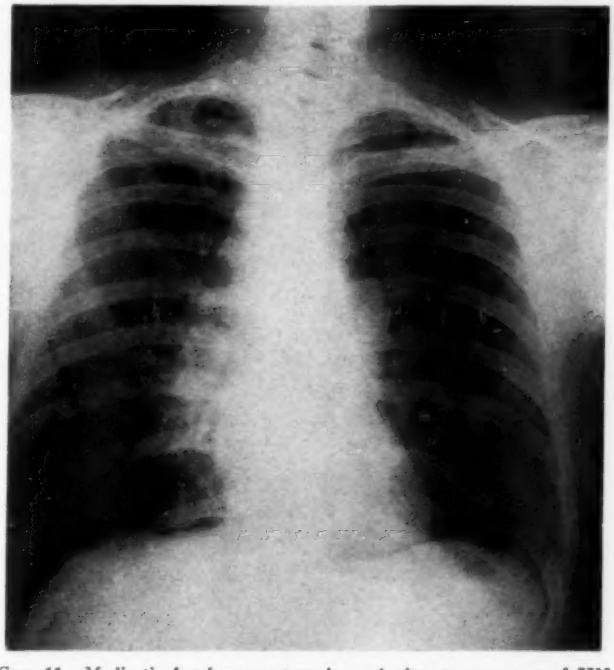

Fig. 11. *Case 11.* Mediastinal enlargement unchanged after two courses of HN_2 therapy.

Discussion

Toxicity. In our group of 52 patients treated with over 100 courses of HN_2, no instance was observed among the patients who died in which it was felt that fatality could be ascribed directly to the drug. Although some patients died within several days after nitrogen mustard was administered, they were all in the terminal stages of their disease, and postmortem examination always revealed adequate cause for death, independently of any possible effect of the nitrogen mustard.

The leukopenia and thrombopenia which occurred were constant causes for concern. However, it was noteworthy that in no instance did complicating infections or agranulocytic angina develop, in spite of white blood counts as low as 500 cells per cu. mm. In fact, the period of maximum leukopenia (8 to 14 days after the beginning of a course of therapy) frequently coincided with the period of maximum well-being in the patient. The leukopenia resembled that seen following roentgen therapy, but was more rapid in

FIG. 12. *Case 11.* Regression of hilar adenopathy following x-ray therapy.

appearance and of shorter duration. Within 24 hours after the beginning of a course of injections of HN_2, there was a fall in the circulating lymphocytes, with a simultaneous rise in the neutrophiles. After 48 to 72 hours, the number of circulating neutrophiles usually began to decline. During the period of greatest leukopenia, a relative, but not absolute, polynucleosis persisted.

The duration of the leukopenia was usually brief, a matter of a few days,

but the severity and duration depended to a certain extent on the level of the white blood count prior to therapy. Patients with counts of 10,000 to 15,000 before treatment usually exhibited a fall to 5,000 to 7,000, whereas patients with pre-treatment counts below 5,000 usually manifested a leukopenia of 1,000 to 2,000. This fall in the white count was considered to be desirable, and was indicative of the inseparable toxic and therapeutic actions of the nitrogen mustard. An absence of marked depression of the white count was interpreted as evidence of inadequate dosage, or of relative resistance to the effects of the drug. Because of the transitory nature of the leukopenia, an initial count as low as 2,000 was not considered as a contraindication for HN_2 therapy. This was true in patients from whom x-ray

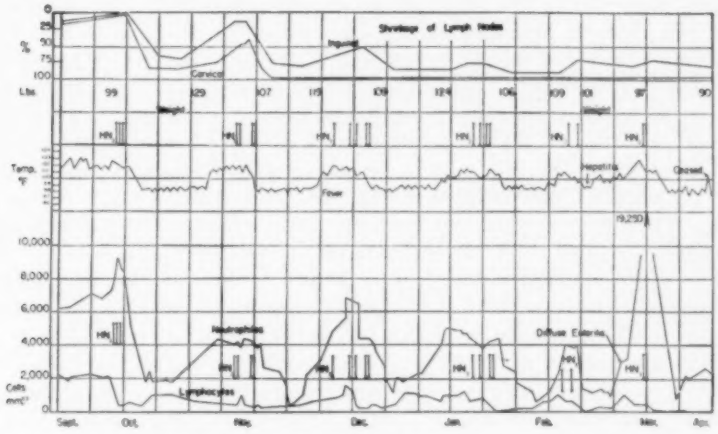

FIG. 13. Clinical course of case 15. Hodgkin's disease, generalized, with pronounced constitutional symptoms. (See illustrative case history.)

therapy was withheld because of the presence of a leukopenia of this degree. If the white blood count remained below 1,000 for more than a few days after treatment, it was sometimes deemed desirable to administer penicillin and intermittent transfusions. It was noteworthy that even after repeated courses of HN_2, with marked depression of the bone marrow, some patients were capable of responding to complications (such as enteritis in case 15) with marked leukocytosis. In most of the patients with Hodgkin's disease, a rapidly rising white blood count preceded the onset of a clinical relapse. From our observations, it appeared that the production of a definite leukopenia may be considered as a requisite for a satisfactory clinical response to nitrogen mustard therapy, and is therefore a useful indication of adequate treatment.

Thrombopenia was a less frequent toxic manifestation than leukopenia, but was more persistent and serious when it did occur. This was usually

the limiting factor in the continuation of treatment in patients with advanced generalized, abdominal or febrile types of Hodgkin's disease, in whom further therapy was often urgently needed. In four cases treatment was discontinued because of the development of purpura. In two patients severe toxic effects on the hematopoietic system were accompanied by total eradication of detectable lymph node enlargement. In general it was felt that in these patients the number and frequency of courses of nitrogen mustard necessary to arrest the disease would also produce a fatal thrombopenia and panhematopenia.

Our clinical findings confirm the experimental evidence in animals that depression of the erythroblastic series occurs less frequently and with less severity than that of the white cell or platelet progenitors. In our series, only two clear-cut instances of anemia induced by HN_2 were observed. However, in many of the patients, a progressive anemia occurred during the period of HN_2 therapy. This was interpreted as being caused by progressive infiltrative disease of the viscera, nutritional factors, or the unknown toxic effects of the disease on the proliferative functions of the hematopoietic system.

One patient (No. 36) with a chronic lymphatic leukemia developed a severe generalized exfoliative dermatitis six weeks after a single course of HN_2. He made a gradual and complete recovery over a two month period. Although it seemed more reasonable to ascribe this complication to the disease in which exfoliative dermatitis is known to occur, it was noteworthy that one other patient who had Hodgkin's disease also developed an erythematous, mildly exfoliative dermatitis two weeks after a course of HN_2.

Another instance of possible nitrogen mustard toxicity, involving the gastrointestinal tract, was that of patient 15, who had generalized Hodgkin's disease. Following four courses of HN_2 therapy during a five month period, with satisfactory clinical response, he developed an intractable, non-bloody diarrhea, nausea and vomiting which persisted for four weeks prior to death. Examinations and cultures of the stools and vomitus were negative. At autopsy the only gross or microscopic findings which were present to account for these symptoms were a few superficial erosions of the lower gastrointestinal tract. Inasmuch as this patient's hematopoietic system showed marked proliferative activity (figure 13) during this episode, it was believed that the HN_2 was probably not the causative factor of the gastrointestinal symptoms.

In this series the routine liver and kidney function tests revealed no impairment following HN_2 therapy.

Evaluation of Therapy

The final evaluation of a therapeutic agent such as nitrogen mustard must necessarily require many years of observation. Nevertheless, certain impressions concerning the clinical usefulness of this drug, with particular

reference to the choice of patients in whom it may be indicated, will be given in the following paragraphs.

In the series of cases reported here, no instance was observed of a favorable response to HN_2 therapy, either symptomatically or in shrinkage of observable neoplastic tissue, in a lesion which was known to be resistant to intensive x-ray treatment; nor was the contrary observed, namely, a lack of some degree of response to HN_2 in lesions known to be radiation-sensitive. This is in keeping with the experimental observation of the similarity in the biological activity of the two agents. However, even though the sensitivity of the malignant lesions to nitrogen mustard and x-ray appeared to be qualitatively similar, the quantitative clinical response to the two agents was often significantly different. In localized lesions which were sensitive to x-ray, maximum destruction of the tumor could be achieved by intensive roentgen therapy. Furthermore, the development of fibrosis and associated impairment of blood supply seemed to inhibit the recurrence of growth and dissemination of the tumor. On the other hand, in disease which was widespread, where local therapy was difficult or impractical, nitrogen mustard was used to better advantage.

With the exception of the three cases of giant follicular lymphoblastoma and two with lympholeukosarcoma, the patients in this series, who had malignant lesions other than Hodgkin's disease, failed to show any remissions greater than four weeks with HN_2 therapy. Since the results in Hodgkin's disease appeared, in general, to be the most favorable, the discussion which follows will be limited to the detailed consideration of the patients with this disease.

Of the 12 patients with focal lymph node involvement, only one showed almost complete shrinkage of the nodes after a single course of HN_2, with a remission which lasted up to six months. In the others, the lymph nodes did not shrink completely and began to enlarge again in three to eight weeks after treatment. Two of these patients responded well to subsequent courses of HN_2 and did not require x-ray therapy. The remaining patients did not exhibit adequate control of the disease with two or three courses of therapy, and intensive radiation was ultimately required to obliterate the local disease. The failure to obtain a satisfactory response in these patients may have been due to inadequate dosage or to our reluctance in continuing the administration of successive courses of HN_2. That repeated courses of nitrogen mustard may in some instances control the peripheral adenopathy of Hodgkin's disease was illustrated in two patients. In case 14, who had bilateral cervical node enlargement, the right side of the neck was treated with large doses of roentgen irradiation and HN_2 was given at the same time. The rate of shrinkage on both sides was approximately the same. After five weeks the left cervical lymph nodes began to enlarge again, and a second course of HN_2 caused them to disappear almost completely. Later the patient developed retroperitoneal lymph node enlargement. The left cervical adenopathy did

not recur during the subsequent eight month period of intermittent HN_2 treatment which was given for the retroperitoneal disease. The patient finally developed marked visceral involvement. Prior to death the lymph nodes in the left side of the neck and in both axillae began to enlarge, but in the right cervical area, which had been treated with intensive roentgen therapy, they remained dormant. In patient 6 who had a retroperitoneal mass as large as a football, rapid and almost complete shrinkage of the nodes followed each course of HN_2 therapy. The recurrences appeared at intervals of two to six months and were controlled with three courses of treatment during a period of 16 months. Since a mild left hydronephrosis developed from pressure on the ureter, he was then treated with roentgen radiation over the abdomen, with complete disappearance of the residual mass. However, five months later, he returned with recurrence of abdominal disease. Although these observations indicate that localized masses can be controlled by sufficiently intensive HN_2 therapy, it does not appear justifiable to use an agent which has as much general toxicity as nitrogen mustard for a purpose which can be accomplished more safely with roentgen radiation.

The reason for the apparent lack of effectiveness in some cases of localized Hodgkin's disease was demonstrated in patient 18, who had a paravertebral lesion at D 12 which did not change after HN_2 therapy, although other areas of involvement responded well. Subsequently he developed a paraplegia, which intensive roentgen therapy over the back failed to relieve. An exploratory laminectomy revealed a fibrosing, infiltrative, epidural Hodgkin's lesion arising from the vertebra, which had appeared normal to x-ray examination. The poor response of the fibrous type of Hodgkin's disease to HN_2 was also demonstrated in three other patients, two of whom had only mediastinal involvement, and the third axillary node enlargement. In each instance biopsy of the nodes which failed to shrink revealed that they were composed largely of fibrous tissue with a relative paucity of cellular elements. In experimental animals it has been shown that obstruction of the blood supply to local areas during the administration of nitrogen mustard effectively protects these tissues from the effect of the drug. This might explain the clinical observation in our cases that in areas of impaired blood supply, due either to fibrosing lesions, previous x-ray therapy, or surgical manipulation in obtaining biopsies, a satisfactory response to HN_2 was not obtained.

Osseous involvement in Hodgkin's disease also responded poorly to HN_2, and in three patients (Nos. 8, 10 and 13) bone disease developed during HN_2 therapy. In patient 13, pain due to multiple vertebral lesions was not effectively relieved during a period of seven months, while he received six courses of HN_2.

The most favorable indications for the use of nitrogen mustard appeared to be in the "occult" febrile type of Hodgkin's disease. Cases 24 to 27 had recurrent febrile episodes for one to three years, with little detectable lymph

node involvement, but with considerable toxicity and progressive weight loss. Prompt relief of fever, malaise, and anorexia, with gain in weight and return of a feeling of well being was obtained with HN_2 therapy.

The least favorable general results were seen in the individuals with advanced visceral and retroperitoneal disease. In only three of these patients (14, 15 and 16) were satisfactory remissions obtained, with lysis of fever and increase in appetite, weight and strength for periods of three to four weeks. One of these patients showed four satisfactory, though short, remissions with HN_2 therapy (figure 13) (see case report). Of the eight unsatisfactory results in this group, six had terminal leukopenia, thrombopenia and generalized purpura. Five of these six patients had persistent panhematopenia prior to HN_2 therapy, hence the drug alone was not responsible for the marked bone marrow depression prior to death. The relative lack of effectiveness of nitrogen mustard in this type of Hodgkin's disease was unfortunate, since roentgen therapy also had little to offer to this group of patients. Nevertheless, a trial of HN_2 therapy in these terminal cases was considered to be amply warranted.

Summary and Conclusions

Nitrogen mustard (methyl bis-betachloroethylamine hydrochloride) was used in the treatment of 52 patients with various types of lymphomas and other neoplastic diseases. Favorable, though temporary, effects were observed in a majority of 27 individuals with Hodgkin's disease, in three with giant follicular lymphoblastoma and in two with lympholeukosarcoma (Sternberg). In the patients with lymphosarcoma, reticulum cell sarcoma, chronic lymphatic leukemia, subacute myeloid leukemia, sarcoidosis and various carcinomas little or no significant beneficial results were seen, even though varying degrees of tumor shrinkage were produced.

In the group of patients with Hodgkin's disease, only two were adequately controlled with repeated courses of HN_2 alone, for periods of more than a year. In 17 individuals x-ray therapy was considered necessary to produce more prolonged remissions than were obtained with HN_2.

Although the most important toxic effects were observed in the hematopoietic system, panhematopenia was only occasionally a limiting factor in the continuation of treatment. The development of a moderate leukopenia was considered as an indication of effective dosage of the drug. Since the leukopenia was usually of short duration, the presence of white blood counts as low as 2,000 per cu. mm. was not considered a necessary contraindication to the use of HN_2 therapy. The occurrence of thrombopenia and purpura was the most serious complication which was encountered.

Nitrogen mustard therapy appeared to be most suitably indicated in the following clinical types of Hodgkin's disease: (1) wide spread involvement which could not be treated adequately with x-ray; (2) individuals with lymphadenopathy and marked constitutional symptoms (fever, weight loss,

etc.); (3) those with fever but without demonstrable enlarged nodes ("occult" febrile type); (4) patients with visceral involvement; and (5) terminal cases which have become "resistant" to roentgen therapy. Radiation was the therapy of choice in patients with relatively localized disease in the peripheral, mediastinal or retroperitoneal regions, with obstructive lesions about the spinal cord, biliary tract, ureters, or great vessels, with bone involvement, and with fibrosing types of Hodgkin's disease (table 2).

TABLE II

Choice of Therapy, Hodgkin's Disease

X-ray	Nitrogen Mustard
1. Localized lymphadenopathy in the peripheral, mediastinal or retroperitoneal regions.	1. Widespread involvement.
2. Bone lesions.	2. Marked constitutional symptoms (fever, weight loss, etc.)
3. Obstructive lesions (great vessels, bile duct, ureters, spinal cord, etc.)	3. Fever without demonstrable enlarged nodes.
4. Fibrosing type of lesions.	4. Visceral involvement.
	5. Lesions "resistant" to x-ray.

ILLUSTRATIVE CASE REPORT

Case 15 (figure 13). *Present Illness:* The patient, a 30 year old white soldier, developed fever and low back pain in March 1946, while in Germany. These symptoms subsided in one week. In May 1946 he began to have persistent dizziness, fatigue and weakness. Several weeks later he also developed backache, fever, chilly sensations and progressive loss of weight. He was hospitalized and returned to the United States, being admitted to Moore General Hospital on July 20, 1946. While there he had a continuous daily fever to 102° to 103°, and a moderate hypochromic anemia. On September 6, a 3 by 5 cm. lymph node was noted for the first time in the right cervical region. This was removed and a diagnosis of Hodgkin's disease was made. The patient was transferred to Walter Reed General Hospital on September 20, 1946.

Physical Examination: The patient was chronically ill, pale and emaciated. He complained of weakness, hoarseness and difficulty in swallowing. Temperature was 100.4°, pulse 100, respirations 18. In the left mid-cervical region there was a 6 by 8 cm. mass of lymph nodes. Another group of nodes, measuring 3 by 5 cm., was present in the left lower quadrant of the abdomen, extending above and below the inguinal ligament. The liver was palpable 3 cm. below the right costal margin, was smooth, firm and non-tender. Paralysis of the left vocal cords was seen by direct laryngoscopic examination.

Laboratory Findings: On admission the red blood count was 3,800,000, hemoglobin 11.6 gm., white blood count 8,200, neutrophiles 78 per cent (stabs 12 per cent), lymphocytes 21 per cent, eosinophiles 1 per cent. Urinalysis was negative. Plasma proteins were 7.5 per cent total, albumin 3.3 per cent, globulin 4.2 per cent. Sedimentation rate was 26 mm. per hour, corrected; hematocrit 41 per cent. Blood urea nitrogen was 11 mg. per cent. Cephalin flocculation test was negative.

X-ray examination of the chest revealed multiple small calcific densities, measuring 2 to 4 mm. in diameter, throughout both lung fields. The hilar lymph nodes were not enlarged. X-rays of the skull, spine, ribs and pelvis were normal. An intravenous pyelogram, performed one month previously, showed anterior rotation of the left kidney.

Histoplasmin, Frei and tuberculin skin tests were negative.

Course in Hospital: The patient was started on a course of HN_3 therapy on October 7, 1946. He was given 0.1 mg./kg. intravenously on four successive days. Three hours after each injection he had nausea and vomiting. On the day following the first injection there was tenderness in the mass of nodes in the left side of the neck, which subsided the next day. The white blood count showed a drop in lymphocytes and a rise in neutrophiles in the first 24 hours (figure 13). Two days after therapy was completed there was an abrupt fall of the temperature to normal, and at the same time a marked drop in total white count, involving principally the neutrophiles. Pronounced shrinkage of the cervical and inguinal lymph node masses occurred within the first week. The symptoms of fatigue and weakness disappeared and the patient became ambulatory. His appetite increased greatly and he gained 30 pounds in 27 days after therapy was completed.

The lowest level of the white blood count was 2,600, with 60 per cent neutrophiles, on the seventeenth day after the beginning of therapy. The lymph nodes reached their smallest size two and one-half weeks after the start of therapy.

Four weeks after treatment the fever returned, the lymph nodes began to enlarge again and the patient began to lose weight. A second course of HN_3 therapy was started on November 14. Two injections, each of 0.1 mg./kg., given on successive days, then the patient was observed for four days to determine whether this amount of the drug would be effective. There was no change in his status and he was given the last two injections. There was a prompt remission similar to that which followed the first course of HN_3. The white blood count, which had risen to 5,100 prior to the beginning of the second course, fell gradually to 1,200 on the nineteenth day after treatment had begun. The patient gained 12 pounds in 20 days, the fever subsided, and the cervical lymph nodes became impalpable. The inguinal nodes did not disappear completely.

On December 10, 1946 fever and enlargement of the inguinal nodes again recurred. It was felt there was probably an enlargement of the retroperitoneal lymph nodes along the left side of the aorta. Three injections of HN_3 were given at intervals of two to three days between December 12 and 20. No change in clinical status occurred. After two more injections, the fever subsided and lymph nodes decreased in size. The white blood count fell from 6,800 to 1,750, with 74 per cent polymorphonuclear leukocytes. The platelet count was 184,000.

Transfusions of whole blood were given about every 10 days after admission to the hospital, and with this regime the patient's red blood count and hemoglobin were maintained at nearly normal levels.

On January 15, 1947, the patient relapsed for the fourth time, with fever, recurrent inguinal node enlargement and a white count of 6,750 per cu. mm. Four daily injections of HN_3, 0.1 mg. per kilo, were given, and the fever again subsided. The patient felt well, but he failed to gain weight. A leukopenia of 1,350 white blood cells per cu. mm. occurred after 14 days. In February 1947, the fifth relapse developed. After two doses of HN_3 jaundice and other signs of liver damage appeared. The possible causes of the hepatitis were considered to be (1) a toxic effect of the HN_3, (2) diffuse involvement of the liver by Hodgkin's disease, and (3) homologous serum (virus) hepatitis. In view of the fact that the patient had received repeated transfusions since August, 1946, it was considered most likely that the hepatitis was associated with these, although the other two possibilities could not be excluded. The patient then developed a persistent non-bloody diarrhea and intermittent vomiting. Smears and cultures of the stools were negative. A leukocytosis of 19,250 cells per cu. mm. developed. On March 18 and 19, during the height of symptoms and fever, two injections of HN_2 were given, and the fever rapidly returned to normal. The white blood count fell to 2,200 per cu.mm. The patient's clinical status deteriorated steadily and he died on April 13, 1947.

Postmortem Examination: There were extensively enlarged lymph nodes in the left retroperitoneal region, extending from the iliac area along the peri-aortic chain to the peri-renal region. These were seen histologically to be due to Hodgkin's disease. No other enlarged lymph nodes were found. The liver showed diffuse necrosis and fatty infiltration. This was compatible with either homologous serum (virus) hepatitis, or toxicity of HN_2. The latter possibility, however, appeared less likely in view of the absence of any other evidence of nitrogen mustard damage. The gastrointestinal tract was normal except for a few small superficial erosions in the small intestine.

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CHRONIC LIVER DISEASE FOLLOWING INFECTIOUS HEPATITIS. II. CIRRHOSIS OF THE LIVER *

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THE relationship of acute infectious hepatitis to cirrhosis has become the subject of considerable discussion at the present time. Most investigators favor the view that cirrhosis may occasionally develop from infectious hepatitis. A lesion resembling the toxic or post-necrotic cirrhosis originally described by Mallory [1] has been recorded by several observers.[2-5] A characteristic feature of this type of "cirrhosis" is a coarsely nodular hyperplasia of liver cells. This picture is very different from the finely nodular liver seen in Laennec's cirrhosis. Lucké [6] has maintained that the apparent increase in fibrous tissue is really due to a compression of the reticulum fibers following the destruction of liver cells, rather than fibrosis. The question of whether or not Laennec's cirrhosis may develop as a result of infectious hepatitis is still being disputed. Bergstrand [2] presented evidence that the post-necrotic type of cirrhosis which he saw in patients with healed acute yellow atrophy sometimes eventually passed into the picture of a finely nodular cirrhosis. Watson and Hoffbauer [7] have recently described a cholangiolitic type of cirrhosis, giving a terminal picture closely resembling classical Laennec's cirrhosis, which developed in patients who had had infectious hepatitis a number of years previously. Sherlock,[8] in a biopsy study of patients with symptoms following infectious hepatitis, found cirrhosis in a few which closely resembled Laennec's cirrhosis. These observations and others [9-13] indicate that several types of sequelae may follow infectious hepatitis but their nature and incidence are not completely clear.

In a previous communication [14] a description was given of the early complications that developed in a group of 400 Navy men who were admitted to the Rockefeller Hospital with acute infectious hepatitis. A few of these men showed clinical evidence of early cirrhosis. The entire group is being followed at the present time and the eventual outcome of the disease in this group will be the subject of future communications. It is hoped that some idea of the incidence of cirrhosis after hepatitis may be obtained from this group.

In addition, a number of servicemen were hospitalized with severe complications of infectious hepatitis who suffered their initial attack in various theatres of World War II. They represented selected patients from a very large number with the disease and it was impossible to draw any conclusions

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regarding the incidence of cirrhosis from this group. However, they demonstrate conclusively that a severe cirrhosis may develop from infectious hepatitis and furnish certain data regarding the type of this cirrhosis.

The group to be discussed includes four servicemen and, in addition, one 18-year old girl. The diagnosis of infectious hepatitis can never be made with absolute certainty. However, the patients in this group represented selected individuals who developed a sudden onset of jaundice associated with gastrointestinal symptoms at a time when they were young and in good health. Two of the five offered a history of contact; the remainder were servicemen whose illness appeared to be a part of the wartime epidemic of infectious hepatitis. A number of other servicemen with chronic liver disease were not included in this series because of the absence of a history of an acute episode of jaundice and because of a complicating factor such as chronic alcoholism.

Autopsy or laparotomy biopsy material was available in each case. Four of the five patients were observed at the Rockefeller Hospital for more than one year and considerable clinical data regarding the progress of the disease were obtained. In view of the fact that the clinical findings in these patients with cirrhosis after infectious hepatitis differed in certain respects from those found in classical Laennec's cirrhosis, they will be discussed in some detail along with the pathological findings.

Case Reports

Case 1. A male, aged 34. In April 1942 shortly after entry into the Army, the patient was vaccinated with an icterogenic batch of yellow fever vaccine. Approximately 10 weeks later he suddenly became ill with acute symptoms of fever, anorexia and vomiting followed by deep jaundice. A number of other men in his company who had been vaccinated at the same time also became jaundiced. He rested in his quarters for two days but because of special combat maneuvers he was forced to resume full activity despite his jaundice. The jaundice gradually decreased over a period of approximately one month but marked fatigue and liver tenderness persisted. For two years liver tenderness and aching over the liver were constant complaints. In June 1945 he was first seen at the Rockefeller Hospital. At this time liver tenderness was no longer so marked a symptom as previously but the patient remained very conscious of his liver. Chronic fatigue and lack of appetite were the chief complaints. Physical examination showed a well nourished young man with a slight icteric tint to the sclerae. One large spider angioma, 3 inches in diameter, was visible over his left shoulder. Ten others were also clearly evident. The upper portion of the abdomen was distended as the result of a very large firm smooth liver extending six fingers'-breadth below the costal margin and a large spleen four fingers'-breadth down. There was no ascites or edema. Liver function showed marked impairment which was most apparent from a serum albumin level of 2.7 gm. per cent. The white blood count was 3800.

The patient was followed in the Out-Patient Department of the Rockefeller Hospital for almost one year during which time he received intravenous liver extract injections twice weekly and a high caloric, high protein diet. Slight improvement occurred on this regime and the patient returned to part time work. Liver function tests did not improve, however. Suddenly in May 1946 the patient developed a sharp

rise in the serum bilirubin level. This was unexpected, and the development of an obstructive lesion on top of the cirrhosis was suspected. An operation was performed but the biliary tract was considered to be normal. The bilirubin continued to climb and the patient died in cholemia in August 1946.

At autopsy the liver was found to be large and cirrhotic. Uniformly sized nodules 0.5 to 1 cm. in diameter could be felt beneath the capsule which projected only slightly. A small stone was found in the ampulla of the common duct which caused complete obstruction. It appeared to have been lodged there for a relatively short time and accounted for the sudden and unexpected rise in the serum bilirubin two months before death. On microscopic examination the liver parenchyma was seen to be divided into rounded islands of liver cells by dense bands of collagenous connective tissue (figure 2). The connective tissue was in large part poor in cells but in some sites, immediately adjacent to the islands of liver cells, collections of lymphoid cells were found. The bile ducts did not show dilatation and there was scant new formation of bile ducts. The fibrous tissue showed little relation to the bile ducts.

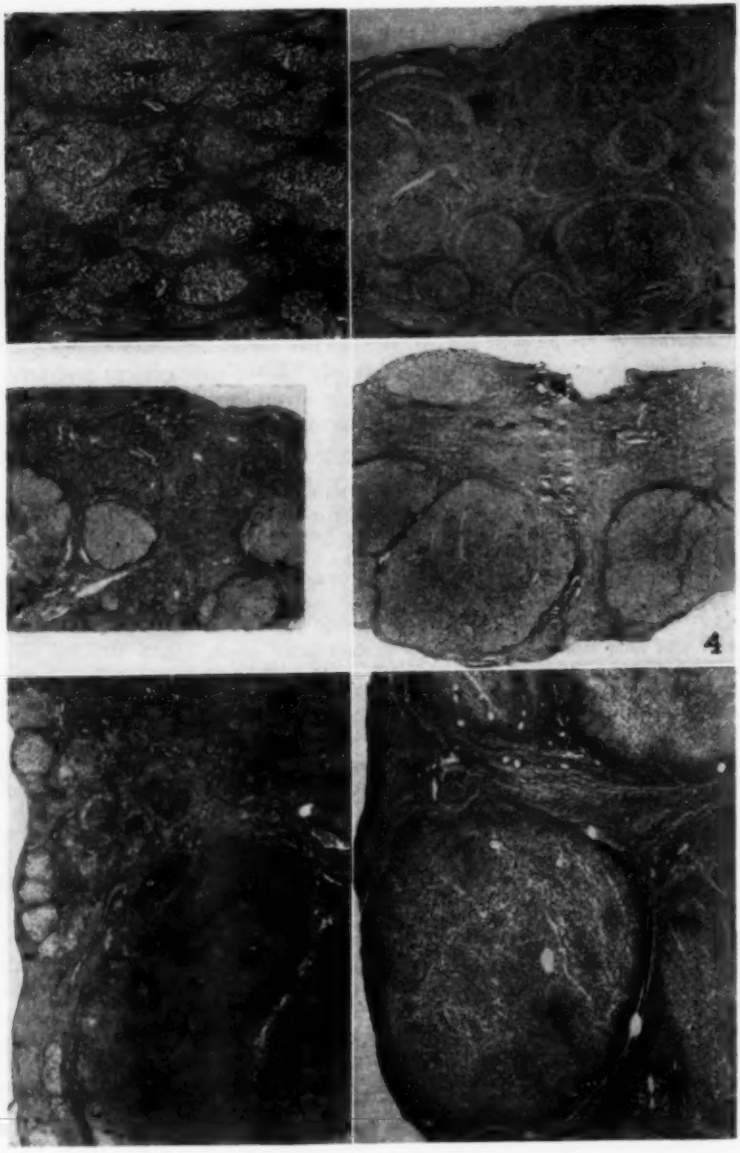
Summary. A 34 year old Army man had serum hepatitis in April 1942 from which he never completely recovered. Liver enlargement and tenderness persisted with marked aberration in liver function tests. Death occurred four years after the onset because of a biliary tract complication on top of his previous liver disease. Autopsy showed evenly nodular cirrhosis.

Case 2. A female, age 19. In May 1941, at a time when two other children in the same apartment house were jaundiced, the patient developed an attack of marked nausea and loss of appetite that was followed by intense jaundice. She was severely ill and was taken to the hospital for two weeks. Her liver was enlarged two fingers'-breadth below the costal margin and tender. The anorexia disappeared after a period of approximately two weeks. The jaundice gradually subsided over a period of 10 weeks. During the next three years the patient had no complaint except occasional episodes of mild jaundice associated with dark urine which usually followed periods of over-activity. These episodes occurred approximately every two months.

In December 1944 the patient went to a physician because of her failure to begin menstruation. He gave her a course of estrogen treatment that was followed by a severe attack of jaundice. Some swelling of the abdomen was noted at this time. The jaundice subsided over a period of two weeks. During 1945 she went to numerous physicians because of her failure to menstruate. Moderate abdominal swelling was noted on several occasions.

In November 1945 the patient developed a sudden massive hematemesis and was admitted to the Rockefeller Hospital. Despite the administration of three transfusions to replace the blood lost, ascites began to accumulate. This gradually disappeared over a period of three months on a nutritious diet. Physical examination showed no spider angiomata. The liver was not palpable but the spleen could be felt three fingers'-breadth below the costal margin. Liver function tests showed marked abnormalities. Bromsulfalein retention was 40 per cent and the serum albumin level was 2.2. gm. per cent. White blood count was 3,100, platelet count 80,000. During 1946 the patient was followed in the Out-Patient Department while attending school. She had no complaints of any sort. In October 1946 the patient developed a second massive hematemesis with the loss of a large amount of blood. She was readmitted to the hospital in coma. After one week of vigorous transfusions and glucose therapy she gradually came out of coma without residual effects. Ascites again developed which rapidly disappeared following injections of concentrated human serum albumin.

In December 1946, a laparotomy was performed with biopsy of the liver. During 1946 and 1947, the patient suffered three more hemorrhages with a second episode of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coma. Spleno-renal anastomosis was performed in May 1947 with complete relief from hemorrhages for over 17 months to the present time.

The gross appearance of the liver was viewed on two occasions. It was extremely small; estimations placed it at approximately one-fourth the normal size. Eight or 10 nodules approximately 1.5 cm. in diameter could be palpated and seen projecting from the surface of the liver. Some areas of the surface showed no nodules. Blocks of tissue were obtained from two different areas of the liver (figure 1 (3) and 2)). On microscopic examination large areas of fibrous tissue were visible with occasional round islands of liver cells. In some places areas of fibrous tissue 2 cm. across were visible without any parenchymal cells. The fibrous tissue was very cellular, consisting chiefly of fibroblasts and lymphocytes and appeared to represent both collagenous connective tissue and contracted reticulum. Numerous newly formed bile ducts were also visible. The islands of parenchyma showed swollen granular cells. Lymphoid cells were abundant at the margins of parenchyma.

Summary. A 19 year old college girl suffered a severe acute attack of infectious hepatitis in 1941 followed by intermittent episodes of jaundice during the next three years. Five esophageal hemorrhages occurred during 1946 and 1947 which were followed by ascites and two episodes of coma. Laparotomy with biopsies of the liver six years after the onset of her illness showed replacement of most of the liver parenchyma with cellular fibrous tissue containing a few round islands of liver cells.

Case 3. A male, age 20. In June 1945, shortly after entry into the Navy, the patient developed an episode of fever, anorexia and nausea that was followed six days later by jaundice. The symptoms were mild and had completely disappeared when the jaundice became evident. He remained in bed for one week. The jaundice subsided rapidly and the patient was able to go through special training without complaints.

In December 1945, four and a half months after the disappearance of jaundice, the patient developed a severe attack of diphtheria with high fever. He was treated in a Navy hospital with penicillin and antitoxin. He was not given any human blood components. While convalescing from this attack two weeks after the onset, he was noted to be jaundiced. This had developed insidiously without any symptoms referable to the liver or gastrointestinal tract. He was forced to remain in bed although he felt well. The jaundice decreased very slowly over a period of three months. His liver was easily palpable. He remained in Navy hospitals throughout 1946 because of marked fatigue that had developed. Liver function tests remained ab-

FIG. 1. Sections of liver (hematoxylin and eosin) × 12 from each of the patients illustrating chiefly the comparative size of the nodules of regenerated liver cells.

(1) Case of alcoholic cirrhosis. Even distribution of fibrous tissue among clumps of liver cells. Shown for purposes of comparison.

(2) *Case 1,* post-hepatitis cirrhosis. Small nodules of liver cells separated by bands of fibrous tissue in a regular pattern. The lesion resembles that of Laennec's cirrhosis.

(3) *Case 2,* post-hepatitis cirrhosis. Islands of closely packed hyperplastic cells in broad areas of contracted reticulum and fibrous tissue. Very little resemblance to classical Laennec's cirrhosis.

(4) *Case 3,* post-hepatitis cirrhosis. Somewhat larger islands of closely packed liver cells surrounded by dense areas of fibrous tissue.

(5) *Case 4,* post-hepatitis cirrhosis. Small and large masses of liver cells separated by dense fibrous tissue bands. Completely irregular pattern of distribution of fibrous tissue and liver cells.

(6) *Case 5,* post-hepatitis cirrhosis. Huge nodules of regenerated liver cells separated by bands of fibrous tissue. Terminal necrosis of many of the liver cells in the nodules.

normal although the jaundice disappeared. He was treated with all known types of therapy during the year without improvement.

In February 1947, 20 months after the onset of his illness, he was admitted to the Rockefeller Hospital. Physical examination showed numerous small spider angiomata over his skin; 60 were counted during one examination. The liver was very firm, smooth and enlarged four fingers'-breadth below the costal margin. The spleen was just palpable. No ascites or edema was present. Liver function tests revealed marked impairment of liver function with 31 per cent bromsulfalein retention and a serum albumin level of 3 gm. per cent. He was treated at the hospital for five months with liver extract, concentrated human serum albumin and a high protein diet. Some improvement in his fatigue occurred but liver function remained unchanged.

A laparotomy was performed in August 1947 and a biopsy of the liver was obtained. The surface of the liver showed a scattering of hard nodules with large areas entirely free of nodules. Most of the nodules were small but one was noted to be 1.5 cm. in diameter. On microscopic examination the liver was found to consist of dense fibrous tissue stroma surrounding a few scattered islands of liver cells (figure 1 (4) and 5)). The islands of parenchymal cells were very variable in size and contained swollen granular cells. The fibrous tissue was quite cellular with numerous fibroblasts, lymphoid cells, and a few polymorphonuclear cells. Numerous bile ducts and blood vessels were also visible in the fibrous tissue.

Summary. An 18 year old Navy man suffered a typical mild attack of acute infectious hepatitis. An attack of diphtheria five months later caused a return of jaundice followed by persistent symptoms and signs of severe liver involvement. Laparotomy biopsy taken two years after the onset showed a hard liver with nodules of various sizes projecting from the surface. Broad dense bands of connective tissue surrounded both large and small islands of parenchyma.

TABLE I

Results of Certain Liver Function Studies Carried Out on the Serum of the 5 Patients with Post-Hepatitis Cirrhosis

Case No.		Bilirubin	Bromsulfalein Retention	Total Lipids	Cholesterol Ratio F/T	Proteins		Thymol Turbidity	Gamma Globulin (Zinc Turbidity)	Prothrombin % Normal	Cephalin Flocculation	Alkaline Phosphatase
						Albumin	Globulin					
		mg.%	%	*mg.%*		*gm.%*	*gm.%*	*units*	*units*			*units*
	Normal range	0.5–1.0	0–4	450–650	<.30	4	2.5	0–4	6–12			
1	June 6, 1945	3.8	37	545	—	2.8	3.0	11	—	70	++++	12
	Dec. 12, 1945	5.0	31	600	.51	2.5	3.0	10	—	—		—
	Aug. 23, 1946	25.0	—	500	—	2.4	4.2	12	32	—	+++	—
2	Jan. 1, 1946	1.2	30	—	—	2.5	4.3	25	38	—	+++	—
	Jan. 3, 1947	1.2	28	—	.45	4.4	3.7	18	34	—		18
	June 29, 1948	0.8	42	420	—	2.8	3.6	13	32	—	+++	—
3	Feb. 3, 1947	1.0	31	450	.41	3.0	4.4	29	58	80	++++	10
	July 21, 1947	1.2	27	—	—	3.0	5.1	20	56	—		—
	Mar. 16, 1948	0.9	27	480	.39	4.1	4.0	16	41	—		—
4	July 31, 1944	3.1	30	900	.61	3.8	3.5	—	—	100	++++	—
	Dec. 1, 1944	3.5	37	675	.40	4.1	3.7	—	—	95	+	—
	Nov. 19, 1945	12.2	31	350	.55	1.8	4.0	18	—	60	++++	4
	May 27, 1946	11.6	29	340	—	2.6	3.7	17	51	46		—
	Nov. 5, 1946	25.0	—	280	—	2.3	3.8	16	48	30		—
5	Oct. 10, 1945	1.5	20	—	—	4.1	3.8	—	—	—	++++	—
	Nov. 11, 1946	12.5	27	220	.48	1.8	5.2	24	65	60		6

Case 4. A male, age 32. In January 1944 while on board ship in the Pacific theatre, the patient developed a typical mild attack of infectious hepatitis with anorexia, nausea and diarrhea. Several shipmates also had a similar illness. The patient had an important assignment and was forced to continue work. Despite the lack of bed rest therapy, some improvement in the patient's condition occurred. Two months

FIG. 2. *Case 2.* Mallory connective tissue stain × 62. Island of closely packed liver cells in a dense area of fibrous tissue and reticulum.

after the onset only slight jaundice remained and the patient felt well. His ship put into port and he went on weekend leave during which time he did a moderate amount of drinking. He returned to his ship with renewed symptoms of anorexia and nausea which were followed by increased jaundice. A definite relapse had occurred. Very little improvement was noted following the relapse and the patient felt very fatigued.

The jaundice remained unchanged. He was admitted to the Rockefeller Hospital in July 1944, six months after the onset. Physical examination showed a well developed young man with definite jaundice. The liver was palpable one finger's-breadth below the costal margin and slightly tender. No edema or ascites was present. Liver function tests showed a bilirubin of 6 mg. per cent and a 4 +cephalin flocculation. The serum albumin level was normal. White blood count was 6,200.

The patient was kept in the hospital for six months on a high protein, high caloric diet with supplementary liver extract injections. A slight fall of his bilirubin level to 3 mg. per cent occurred immediately. However, no further improvement developed Fatigue and liver tenderness continued along with marked bromsulfalein retention. He finally left the hospital against advice and attempted to do work as a salesman. Six weeks after discharge his bilirubin had risen to 7 mg. per cent, and symptoms of weakness and fatigue had grown progressively worse.

In August 1945, seven months after discharge, edema of the ankles appeared. This was followed by ascites one month later. He was finally readmitted to the hospital in November 1945 in a terminal state with marked edema of his legs and back and a large amount of ascites. A marked change in the condition of the patient had occurred in the 10 months between admissions to the hospital. He was now very thin and emaciated. The liver was palpable four fingers'-breadth below the costal margin and was hard and irregular. One large nodule was clearly palpable. The spleen was three fingers'-breadth below the costal margin. Jaundice was much increased. The outstanding change in liver function tests was that his serum albumin level was depressed to 1.3 gm. per cent. The white blood count was now 3,400.

Following admission to the hospital after receiving three paracenteses, he was treated with 27 units (25 gm. per unit) of concentrated human serum albumin. This therapy brought about remarkable improvement with complete loss of edema and ascites and a feeling of well being with excellent appetite. The improvement, however, was only temporary and further albumin injections were necessary to control the edema and ascites. Liver function showed no change and the proteins formed by the liver were all very low. The prothrombin time was 40 per cent of normal and the fibrogen was 140 mg. per cent. The patient suffered from a severe bleeding tendency from his nose and gums that could be controlled only by numerous transfusions. He finally died because of slow loss of blood despite 19 transfusions. His bilirubin level showed a progressive rise to 26 mg. per cent (figure 1). His second period of hospitalization lasted 12 months. During this time his liver was palpated very frequently and it was noted by numerous observers that the liver gradually decreased in size and that the large hepatic nodule that was readily palpable during the early months of his admission was no longer palpable.

At autopsy the liver was enlarged, weighing 1,500 gm. Figure 7 shows a cross section photograph. The surface was somewhat nodular but not hobnail in appearance. The nodules were quite variable in size ranging from 0.2 cm. to 2 cm. in diameter. On microscopic examination, dense bands of collagenous connective tissue, in large part poor in cells and bile ducts, were visible which divided the parenchyma (figure 1 (5) and 4)). Some areas of fibrous tissue contained numerous dilated blood vessels. Wide areas of parenchyma showing little penetration by fibrous tissue were also seen. In these areas most of the cells were well preserved but many were without nuclei and there appeared to be early foci of necrosis of liver cells.

Summary. A 32 year old Navy man developed epidemic hepatitis aboard ship where he continued to work. A relapse followed a shore leave two months after the onset. No improvement occurred after six months of treatment in the hospital. Edema and ascites developed when work was

attempted. Ascites was controlled by albumin injections but liver function became progressively worse and the patient died from bleeding gums three years after onset of his disease. Autopsy showed a liver that was irregularly nodular. Dense bands of fibrous tissue surrounded both small and very large areas of parenchyma.

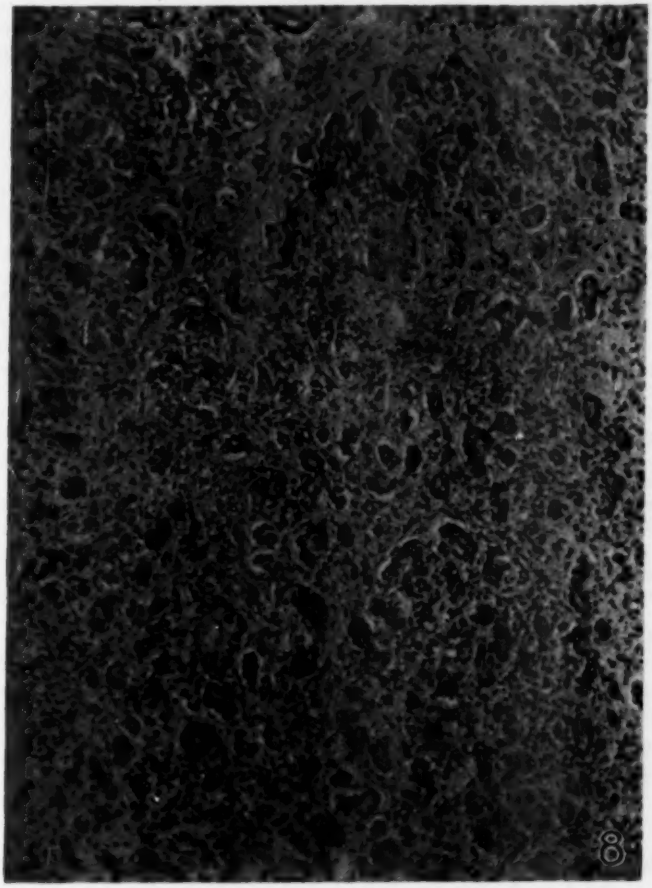

FIG. 3. *Case 5.* Hematoxylin and eosin × 135. Numerous regenerating bile ducts and cellular fibrous tissue which made up the broad areas between islands of liver cells.

Case 5. A male, age 19. One month after entrance into the Navy the patient became acutely ill with a temperature of 105° and marked symptoms of vomiting and general malaise. He was admitted to a Naval hospital. His white count was only 5,600 and he was critically ill. Because hemolytic streptococci were found in his

throat, he was started on penicillin therapy with some improvement. Six days after the onset of his symptoms he was noted to be jaundiced. His cephalin flocculation was 4 + at this time. The jaundice gradually decreased over the next three weeks but the cephalin flocculation remained 4 +. The liver was not palpable at any time but the spleen was enlarged. He showed marked symptomatic improvement but because of the persistently positive cephalin flocculation test and an anemia (3.5 million red blood cells) he was kept in the hospital for six months. During this time he had marked fatigue, some bleeding of his gums, and several episodes of petechial hemorrhages. He was finally given a medical discharge in December 1945 with the diagnosis of chronic hepatitis. He returned to his home but was unable to work. He tired easily and slept a great deal. His parents noticed that his eyes were always slightly yellow. During the summer of 1946 his fatigue and jaundice increased and he began to lose weight rapidly. In September 1946 ankle edema appeared followed by ascites one month later.

He was readmitted to the hospital in October 1946 because of marked ascites. Four paracenteses were carried out over a period of six weeks. He also developed two large hemorrhages while in the hospital that were treated by six blood transfusions. He was transferred to the Rockefeller Hospital in November 1946. Physical examination showed a thin, chronically ill man. Marked jaundice, edema and ascites were apparent. Numerous spider angiomata were visible over the left forearm, neck and shoulder. The liver was not palpable but the spleen was felt two fingers'-breadth below the costal margin. Liver function tests showed extreme impairment with a serum albumin level of 1.8 gm. per cent. Six days after admission he suffered a severe esophageal hemorrhage and lapsed into coma. Despite blood, plasma and albumin transfusions, he died. At autopsy the liver was found to be very small and shrunken. Numerous nodules were apparent projecting from the surface, some as large as 4 cm. while others were less than 0.5 cm. Most of the liver, however, consisted of tough fibrous tissue with no apparent liver cells. On microscopic examination, the nodules were found to consist of masses of liver cells with no lobular pattern (figure 1 (6)). The central portions of these nodules showed large areas of necrotic cells. The cytoplasm was still recognizable and some nuclei persisted. This tissue was in sharp contrast to well preserved parenchymal cells at the margins of the nodules. Surrounding the nodules was a dense area of collagenous connective tissue with many cells of the lymphoid type and numerous new bile ducts (figure 3).

Summary. A 19 year old Navy man developed epidemic hepatitis complicated by a streptococcus infection. He never recovered entirely and marked liver function aberrations developed. Finally severe ascites and numerous esophageal hemorrhages led to his death 17 months after onset. Autopsy showed a few huge irregular nodules of regenerated liver cells and dense areas of fibrous tissue completely devoid of liver cells.

Discussion

The exact reasons why infectious hepatitis deviated from its usual benign course and led to the development of cirrhosis in the five patients discussed above are not completely clear. However, certain of the factors involved are apparent from the histories of these patients. First, activity during the acute stage of infectious hepatitis was important in two of the patients (Nos. 1 and 4) who continued wartime duties despite severe jaundice. The importance of rest during the acute and convalescent stages of infectious hepa-

titis was emphasized by numerous investigators during the recent war.[14, 15] One of these patients suffered a relapse during convalescence with a return of jaundice following a shore leave during which he consumed alcohol. The patient did not receive adequate care until he had had his illness for five

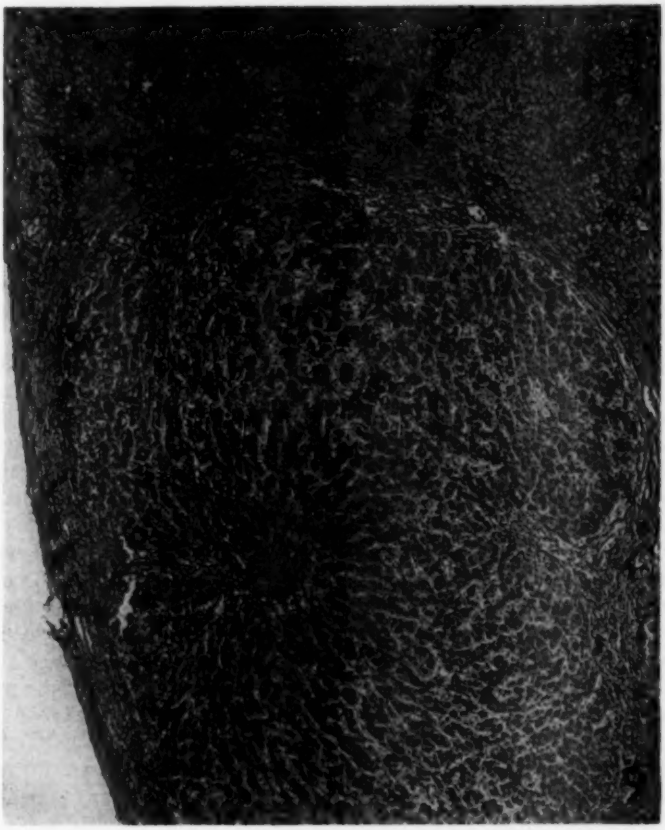

FIG. 4. *Case 4.* Hematoxylin and eosin × 62. Nodule of liver cells surrounded and invaded by fibrous tissue. Loose, highly vascular reticulum surrounds the area.

months. Marked liver function abnormalities had developed which failed to respond to treatment at that late date.

A second factor possibly playing a rôle in the development of cirrhosis in the two patients just mentioned was their age. Both of these patients were more than 30 years old which is considerably above the average age of servicemen who contracted infectious hepatitis. The previous study on

chronic hepatitis from this laboratory [14] demonstrated that age was a factor in determining the ability of patients to recover from infectious hepatitis. Patients over 30 were more prone to develop chronic liver disease than those in younger groups.

A third factor which appeared to play an important rôle in the development of cirrhosis in two of the other three patients (Nos. 3 and 5) was a severe bacterial infection complicating infectious hepatitis. In one patient a streptococcal infection of the throat with high fever developed during the acute stage of infectious hepatitis. The patient was critically ill and he never recovered from the initial episode. The second patient suffered a severe attack of diphtheria four and a half months after recovery from a mild uneventful attack of infectious hepatitis. This brought about a return of jaundice and the patient never recovered from his liver disease although the diphtheria subsided uneventfully.

In four of the five patients, therefore, definite factors were apparent which probably contributed to the development of cirrhosis. These observations suggest that when cirrhosis of the liver develops after infectious hepatitis complicating factors are almost always involved.

The clinical picture of cirrhosis was quite variable in the five patients under discussion. In two of the patients the dominant manifestation of the disease was frequent esophageal hemorrhages. Determination of the portal pressure in one of the patients at operation showed that it was markedly elevated. Porto-caval anastomosis in this patient brought about a cessation of hemorrhages. Edema and ascites were also prominent clinical manifestations in these two patients but they developed as a result of blood loss from hemorrhage. A defect in protein synthesis existed which did not become evident with the formation of ascites and edema until after depletion of body proteins by hemorrhage. A third patient in the group showed severe generalized edema and associated ascites as the primary manifestation of his disease. Serum albumin levels were as low as 1.4 gm. per cent. Prothrombin and fibrinogen values were also very low. As a result the patient suffered from bleeding from his mucous membrane that eventually led to his death. The edema and ascites were readily controlled by injections of concentrated human serum albumin. The abnormality in the proteins formed by the liver in this patient was extreme and was greater than in any patient seen at the Rockefeller Hospital suffering from other types of cirrhosis of the liver.

In all of the patients of this series the primary aberrations in liver function were those related to protein metabolism. In each case a depression of the albumin concentration in the serum was apparent early in the course of the disease. This was strong evidence for the concept that the cirrhosis was the result of primary liver cell damage. None of these patients showed evidence of intrahepatic biliary obstruction with the development of cholangiolitic cirrhosis similar to that described by Watson and Hoffbauer [7] following infectious hepatitis. Severe jaundice was a late manifestation and

was not associated with elevated values for serum lipids and alkaline phosphatase.

Another characteristic feature of the protein picture in these patients which also indicated primary cellular damage to the liver was a marked abnormality in the globulin fraction of the serum. This was partially evident

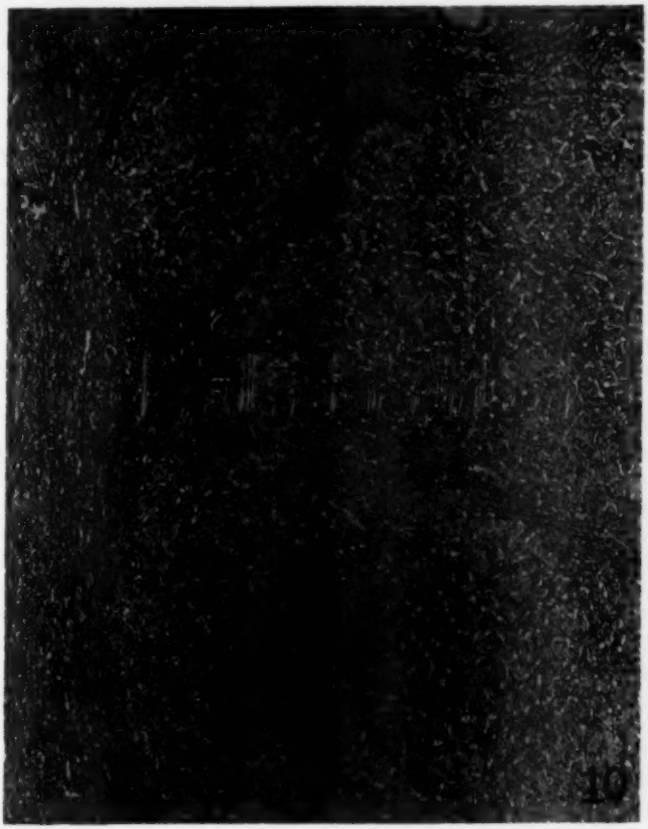

FIG. 5. *Case 3.* Hematoxylin and eosin × 62. Small and large nodules of closely packed granular liver cells surrounded by contracted reticulum and some fibrous tissue.

from the very positive cephalin flocculation and thymol turbidity reactions obtained in all of the patients. The average value for the thymol turbidity reaction in these patients was far above the average value obtained in a group of patients with true Laennec's cirrhosis.[16] Estimations of serum gamma globulin also revealed high values. The unusual degree of globulin aberra-

tion aided in classifying the cirrhosis in these patients as differing from other more common types of cirrhosis.

Certain unique features were also apparent on physical examination. Two of the patients demonstrated a very large number of spider angiomata over the neck, shoulders, arms and chest. Some of these vascular anomalies were 4 to 5 cm. in diameter and were unusually prominent. Four of the five patients also showed marked enlargement of the liver. This was particularly true of patients 1 and 4 who had enlargement of such a degree that protuberance of the upper abdomen was readily apparent in the erect position. Patient 1 showed a number of changes in the condition of his liver as observed on physical examination during the three years that he was observed. During the first year following the initial attack of infectious hepatitis the liver was moderately enlarged, smooth and quite tender. At this time liver function was only slightly impaired. During the second year a readily apparent irregular nodular enlargement developed. The border of the liver extended almost to the iliac crest and one nodule the size of an egg was palpable. Carcinoma was strongly suspected at this time. Gradually during the third year of observation the nodule became no longer palpable and the liver decreased in size until it was only a few centimeters below the costal margin. It appeared as if the hyperplastic nodules had decreased in size along with general shrinkage in the size of the liver.

Another characteristic feature of the physical examination in these patients was marked enlargement of the spleen. The degree of enlargement appeared greater than is usually seen in other types of cirrhosis. Along with the splenic enlargement four of the five patients were found to have a white blood count below 4,000. These patients also showed considerable anemia but this is somewhat difficult to evaluate in view of the associated bleeding. Two of the patients demonstrated a marked platelet deficiency. This disappeared in patient 2 following splenectomy. It was apparent that these patients demonstrated all of the characteristic features of a Banti's syndrome with definite "hypersplenism" in at least one of the patients. This raises the question as to whether many of the younger individuals classified in the past under Banti's syndrome may not have developed such a picture as a result of infectious hepatitis.

The most characteristic feature of all, however, in the clinical course of these patients was the progressive nature of the disease once cirrhosis became established and its lack of response to therapy. Three of the patients died despite treatment in the hospital for more than one year with all known forms of therapy. Only one of the patients remains in a relatively stable state at present. No improvement in bromsulfalein retention or the protein abnormalities of the serum occurred in any of the patients following therapy. (The albumin level of the serum was raised artificially by albumin injections but this was purely a temporary effect.) This is in distinct contrast to the effect of nutritional forms of therapy in the ordinary types of cirrhosis fol-

lowing chronic alcoholism. In the latter, prolonged therapy over a period of one year often brings about complete improvement in the condition of the patient and improvement in the abnormalities in bromsulfalein retention and serum proteins.[17]

The pathological material from the patients with cirrhosis after infectious hepatitis demonstrated certain distinguishing features not usually seen in the classical Laennec's type of cirrhosis. Four of the five cases could readily be differentiated both in the gross and the microscopic specimens. The characteristic feature was the presence of large nodules of regenerated liver cells some of which projected from the surface of the liver, while others formed islands embedded in dense areas of fibrous tissue. The nodules were very variable in size ranging from minute clusters of liver cells to round

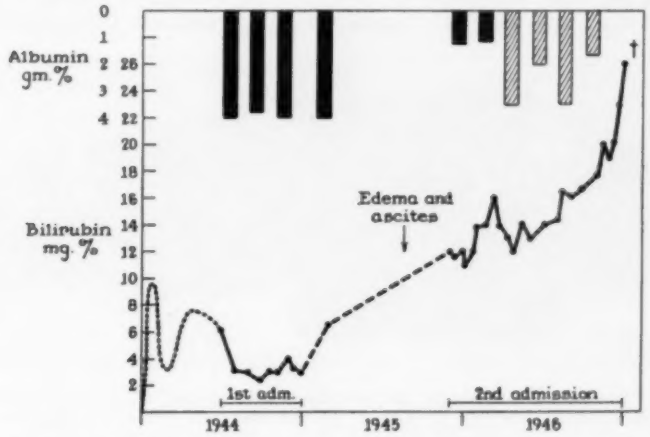

FIG. 6. *Case 4.* Serial determinations of serum bilirubin and serum albumin during the three-year period between the initial attack of infectious hepatitis and death. The shaded albumin columns represent values after intravenous albumin therapy.

masses 4 cm. in diameter. The cells in these nodules were hyperplastic and closely packed in no orderly lobular pattern. The blood supply of these cells appeared poor and in two of the cases the central part of some of the nodules showed fresh necrosis of the liver cells, a result that appeared to have developed terminally. Fibrous tissue was present partly as dense bands of collagenous connective tissue which surrounded the nodules of liver cells but also as what appeared to be contracted reticulum completely devoid of liver cells. The greatest part of the liver consisted of the latter type of tissue. Fibroblasts, mononuclear cells and numerous newly formed bile ducts were found in these areas which extended for as far as 6 cm. without any liver cells. Different portions of the liver showed widely different appearances. This was in contrast to the regular pattern of bands of fibrous

tissue intertwined among small areas of liver cells usually seen in Laennec's cirrhosis.

The cirrhosis in these cases closely resembled the lesion originally described by Mallory [1] and called toxic cirrhosis or healed acute yellow atrophy. This was recognized to follow in a few cases of severe acute damage to the liver where recovery from the acute episode occurred. The initial attack, however, in the four cases described in the present group was mild and did not differ from that in other cases of infectious hepatitis where complete recovery occurred. Clinically the cirrhosis appeared to be a progressive process over a long period of time which is somewhat difficult to reconcile with the pathological findings suggesting healing from an unusually severe acute process. It is possible that the severe damage which caused regeneration of liver cells in isolated nodules occurred during the period of relapse but the exact time when the unusual lesion developed was not apparent clini-

FIG. 7. *Case 4.* Cross-section of the liver obtained at autopsy. A few large nodules are visible projecting from the cut surface. In some areas the nodules are much smaller.

cally. That this lesion does not remain static was clearly evident from the marked reduction in the total size of the liver and variation in the clearly palpable nodules that occurred with time in at least one of the patients.

Each of the four cases demonstrating irregular nodular hyperplasia showed considerable variation in the size of the nodules and in the amount of fibrous tissue free of liver cells. At one extreme was the liver with large areas of contracted reticulum and fibrous tissue and a few huge nodules, while at the other extreme was the liver showing numerous smaller nodules and narrower bands of fibrous tissue with isolated areas closely resembling the lesion of classical Laennec's cirrhosis. The fifth case in the group showed no large regenerated nodules and the fibrous tissue formed a regular pattern consistent with the picture usually seen in Laennec's cirrhosis. From a study of these five cases it appeared that the picture of Laennec's cirrhosis could develop following infectious hepatitis but that the characteristic lesion resembled the toxic cirrhosis of Mallory.

Conclusions

1. Five patients are described who developed clinical evidence of severe cirrhosis from two to six years after an attack of infectious hepatitis.

2. Associated bacterial infection, strenuous activity during the initial attack and during relapse, alcohol and the age of the individuals appeared to have been contributing factors in the development of cirrhosis.

3. The clinical course of the five patients differed from that usually seen in Laennec's cirrhosis in that the disease was progressive and not materially affected by therapy. Severe abnormalities in various proteins of the serum were also characteristic. The late manifestations of the disease resembled those described in the past under Banti's syndrome.

4. The characteristic pathological lesion was an irregular nodular hyperplasia of liver cells between broad areas of contracted reticulum and fibrous tissue. In four of the five patients the picture differed from that seen in classical Laennec's cirrhosis. Various gradations were seen in the different patients between cirrhosis with huge nodules of regenerated liver cells widely separated by a loose fibrous tissue stroma, to finely nodular cirrhosis with regular formation of islands of parenchyma by bands of fibrous tissue.

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PRIMARY CARCINOMA OF DUODENUM *

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Primary carcinoma of the duodenum has long been known as a rare condition having a reported incidence of .03 to .003 per cent of all autopsies, or one case in 3,000 to one in 31,000 autopsies.

The first report of a case of primary carcinoma of the duodenum is found among the writings of Georginis Hamberger as early as 1746. A second instance of a case was recorded by Giovanni Morgagni in 1761. This was localized in the first portion of the duodenum. Almost a century elapsed before additional instances were recorded. Since the turn of the 19th century, many reports began to appear. While an extensive literature has accumulated on this subject, critical analysis of the cases reported demands that many, especially among the earlier papers, be discarded for the lack of pathologic proof of the diagnosis.

We wish to present two cases of primary carcinoma of the suprapapillary portion of the duodenum, to review briefly the literature in order to emphasize the more important clinical facts and to reëvaluate the statistics relative to the incidence.

Case Reports

Case 1. A 58-year-old white male was admitted to the hospital on August 24, 1945, with the chief complaint of abdominal pain shortly following a meal. These attacks of pain came on almost daily, usually three to four hours after meals and were not relieved by food intake. The pain was of an intense, gnawing, cramping character and located just to the right of the epigastrium and radiated about half way around the right costal margin. There was no associated vomiting or diarrhea. The last attack occurred three days before admission and lasted about one hour. There had been no history of light colored, bloody or tarry stools; no dark colored urine; and no perceptible jaundice. Since the onset of his illness, he had lost his appetite and some 10 to 15 pounds in weight.

His systemic review was essentially negative except for a constant feeling of generalized weakness during the past year. Past history was non-contributory.

Physical examination revealed a well developed, rather obese white male in no apparent distress. The only positive finding was a moderate degree of abdominal tenderness in the right upper quadrant under the right costal margin.

An admission diagnosis of acute cholecystitis and possible gastrointestinal pathology was made. While in the hospital, he had two attacks of abdominal pain. The first occurred on his second hospital day and was similar to the previous attacks of right upper quadrant pain with localized tenderness and a slight amount of spasm. The second attack, which occurred eight days later, was described by the patient as if "a leather belt were tightened around my chest."

Laboratory findings were as follows: Urine, negative; hemoglobin 70 per cent, red blood cells 3.15 M., white blood cells 7,750, with a normal differential. Sedimenta-

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From the Department of Pathology, Montefiore Hospital, Pittsburgh, Penna.

tion rate was slightly increased. Serologic test for syphilis, negative. Cholecystogram revealed normal visualization of the gall-bladder without any evidence of biliary calculi. Gastrointestinal series showed well outlined esophagus and stomach without any evidence of abnormality. The duodenal bulb ballooned out well. A small diverticulum extending from the second portion of the duodenum was observed. Aside from the small diverticulum in the second portion of the duodenum, the upper gastrointestinal tract was reported as negative. A chest film showed normal lung fields and a heart of normal size and configuration. The electrocardiogram presented only minimal changes. The temperature curve was practically flat throughout his stay varying between 97 and 98.6° F. The patient was treated symptomatically and discharged on his fourteenth hospital day (September 7, 1945).

On the day following his discharge, he had a very severe pain starting in the right upper quadrant and radiating to the epigastrium. This was followed by vomiting of coffee-ground material but no bright red blood. This was succeeded by a similar attack the following day. On the day before his second admission into the hospital, he again vomited large amounts of brownish material.

He was readmitted to the hospital 12 days after his first discharge (September 19, 1945) with complaints of vomiting, abdominal pain, and marked weakness. Physical examination revealed a stout white male with marked pallor and slightly labored breathing. Blood pressure was 92 mm. Hg systolic and 54 mm. diastolic; pulse 100 per minute. Examination of the abdomen showed slight epigastric tenderness. Blood count on admission was as follows: Hemoglobin approximately 30 per cent with a red count of 1.30 M. The impression on this admission was either a bleeding peptic ulcer or carcinoma of the stomach. Multiple blood transfusions (eight pints) were given; in spite of this, his blood count remained practically stationary. The bleeding continued and his condition became progressively worse. He became more markedly exsanguinated and died on September 26, the seventh hospital day.

Necropsy was performed an hour after his death. The findings of interest were confined to the abdomen.

Pathological Report: When the abdominal cavity was opened, the stomach, small intestines, and large bowel were found to be greatly distended. The entire length of the intestines showed a bluish discoloration, and on sectioning, a large amount of dark purplish-red blood was found. The stomach cavity contained about 500 c.c. of partially clotted fresh blood. On opening the duodenum, a large circular ulcer with an indurated base and elevated margin was found about 2 cm. from the pyloric ring. The ulcer measured 4 cm. in diameter and occupied approximately two-thirds of the circumference of the duodenum. The ulcer was crater-like in appearance and at the base, there were several openings of moderate-sized vessels which were apparently the source of the massive hemorrhages. On sectioning the ulcer mass, there was definite gross evidence of malignant degeneration. The wall of the duodenum was involved through the muscular layers, but the serosa was smooth with no evidence of perforation or extension outside the duodenal wall. The common duct and the ampulla of Vater were not involved. On the anterior surface of the duodenum, there was a large lymph node the size of a marble. The cut section of the node showed evidence of malignancy.

Sections from the wall of the ulcer of the duodenum showed nests of epithelial cells with tendency to form acini. Most of the cells were poorly differentiated. The nuclei were hyperchromatic with numerous mitotic figures. The tumor cells infiltrated throughout the muscle layers and reached the serosa. The regional lymph node showed almost the entire lymphoid structure replaced by tumor cells. Other parts of the ulcerated area showed large blood vessels with erosion of the wall and moderate inflammatory reaction. Diagnosis: Carcinoma of the duodenum with ulceration and metastasis to regional lymph node (figures 1 and 2).

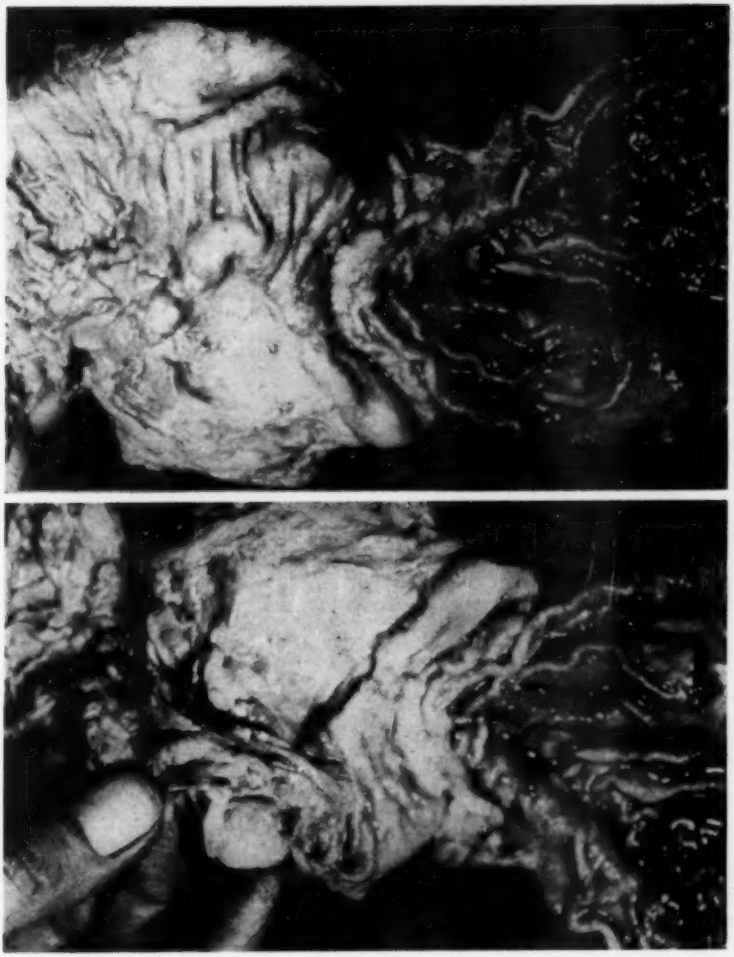

FIG. 1. (*above*) Showing part of the stomach with portion of the duodenum. The tumor is located about 2 cm. from the pyloric ring with an everted margin, necrotic center, eroded blood vessel (pancreatico-duodenal artery). (*below*) Showing the same with dissection of the lumen of the common duct, patency of the lumen, and no involvement with malignancy.

Case 2. A 69-year-old white male was admitted October 25, 1947, with the chief complaint of "stomach trouble." Two weeks before, the patient became nauseated and vomited following a meal. The vomitus was green and sour. He developed diffuse abdominal cramps. An enema yielded black fluid. Since that time he has had marked anorexia and a loss of seven pounds. Weakness was constant.

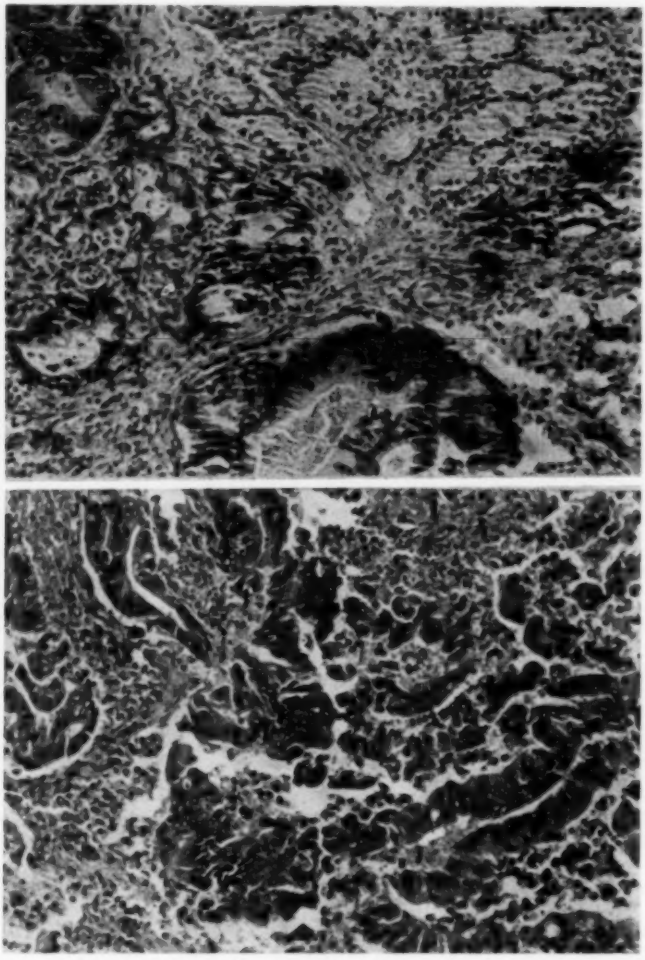

FIG. 2. (*above*) H. & E. ×100. Sections from the duodenal tumor showing a portion of normal duodenal mucosa with Brunner's glands on the upper left and atypical glands lined with hyperchromatic nucleated cells, pleomorphic, and showing numerous mitotic figures. (*below*) H. & E. ×400. Showing adenocarcinoma of the duodenum. The cells are mostly high columnar in type.

Past Medical History: In 1906 to 1912, the patient had "stomach trouble" with fainting, nausea, vomiting, and weight loss. Appendectomy performed in 1912. Renal calculus in 1927. Asthma. Fracture of right ankle.

Family and social history was non-contributory.

Physical examination revealed a well developed and obese white male in no acute distress. His blood pressure was 176/94 mm. Hg; pulse 72 per minute and regular.

There was slight epigastric tenderness. Some weakness of the right arm and hand was noted. The rectal examination was negative. Hemoglobin 13 gm.; red blood cells 4.7 M.; white blood cells 7,860; polynuclears 68; lymphocytes 32 per cent. Sedimentation rate was 6 mm. per hour. Wassermann test was negative. Urine: albumin negative; sugar negative; white blood cells, occasional. Non-protein nitrogen 35; blood sugar 90 mg. per cent.

Gastrointestinal series was normal except for "diverticulum in the second portion of the duodenum on the lesser curvature of the C curve aspect." The chest roentgen-ray was negative. The cholecystogram was entirely negative. The electrocardiogram showed left ventricular hypertrophy.

The patient was discharged with a diagnosis of diverticulum of the duodenum. His second admission occurred on November 18 at 1:15 a.m. The day previous, November 17, he was suddenly stricken with epigastric distress and weakness. He collapsed following a bowel movement which was black in color. No severe pain or vomiting occurred.

An examination revealed a soft abdomen, no masses palpable, and no areas of tenderness. His color was fair, pulse 75 per minute, blood pressure 110/60 mm. Hg, red blood cells 3.8 M., hemoglobin 11 gm., white blood cells 8,000, hematocrit 38 per cent.

On November 19, the patient passed a tarry stool and complained of extreme weakness and mid-epigastric pain. Pulse was 96 per minute, blood pressure 94/68. Several hours later, the patient vomited 50 c.c. of dark blood. His skin was pale, cool, and moist. On November 21, his urea nitrogen was 35 mg. per cent and his prothrombin time was 90 per cent. On November 24, his urine showed a trace of sugar, 4 to 5 white blood cells per high power field, occasional hyalin and granular casts, positive for 1.2 Ehrlich units of urobilinogen. The patient seemed to improve somewhat until November 23, when he vomited coffee ground material twice. Following these episodes, his blood pressure and pulse were not obtainable but could be elicited within five minutes. Blood pressure was 100/70 mm. Hg, temperature 104° F., and pulse 150. Transfusions (three) were given slowly. The patient died on November 24, at 6:20 p.m.

Pathological Report: The pulmonary conus was opened in situ and an antemortem thrombus was discovered which was well formed, cigar-shaped, and firm. It had some branchings suggesting its origin from the veins of the lower extremity. There was some thickening and hypertrophy of the left ventricle. Heart weighed 420 gm. The right lung weighed 330 gm. It was markedly atelectatic. The left lung weighed 420 gm. It too showed a marked atelectasis. The esophagus was opened and the mucosal surface showed superficial erosions and hemorrhage beneath the mucosa. The stomach was filled with about 350 c.c. of dark liquid blood. The pylorus was entirely normal. There were adhesions of the first and second portions of the duodenum, anteriorly to the transverse mesocolon, and posteriorly to the pancreas. On dissection of the transverse mesocolon from the duodenum, a large anterior ulceration of the duodenum was inadvertently entered. There was fibrotic reaction in the mesocolon at the site where it had effectively plugged the perforation. The edges of the perforation were rounded and smooth. This defect was approximately 1.5 by 2 cm. It was situated at the anterior and inferior portion of the duodenum where the first portion enters into the second portion. On the posterior wall, there was a large penetrating cavity which was filled with clot. On removal of this clot, it was seen that the cavity had ulcerated into the head of the pancreas and in the center of the cavity, a sclerotic vessel ran horizontally with an obvious perforation. This was the pancreaticoduodenal vessel and was the source of the gastrointestinal hemorrhage. On further observation, it was noted that both the anterior perforation and the posterior penetrating ulcer were one continuous ulcerating lesion which measured approximately 4 by 4 by 2 cm. The remainder of the duodenum, jejunum, and ileum were filled with

dark brownish-red blood and clots, and their mucosal surface was entirely normal. The head of the pancreas was firm, thickened, and fibrotic especially in that region where the penetrating ulcer had eroded into its substance. The tail of the pancreas was softer and appeared quite normal.

On examination of the left common iliac vein, a large cigar-shaped thrombus measuring about 3 by 1.5 cm. was found within this vessel. This appeared to be antemortem thrombus also and it was considered possible that this was the source of the pulmonary embolus. The opposite common iliac vein was collapsed and contained no thrombus.

Anatomical Diagnoses: 1. Pulmonary embolus. 2. Thrombosis of the left common iliac vein. 3. Exsanguinating hemorrhage from a large posterior penetrating carcinoma at the juncture of the first and second portion of the duodenum eroding the pancreatico-duodenal vessel; and an anterior perforation of the duodenum at this site with effective closure by the transverse mesocolon.

Microscopical Findings: Sections from the ulcer of the duodenum show malignant cells infiltrating throughout the muscular layers and reaching the head of the pancreas. The glands are atypical, lined by hyperchromatic epithelial cells. The tumor cells are independent from the pancreatic acini. Evidently, they originated from the duodenum. Microscopical diagnosis: Malignant ulcer of duodenum (figure 3).

INCIDENCE

In order that the rarity of primary carcinoma of the duodenum be better appreciated, let us first consider a few tables.

Table 1 shows the incidence of primary carcinoma of the duodenum in a number of series of large autopsies totaling 483,695, to be 167 or .035 per cent. Difficulty arises in obtaining accurate statistics because of repetition of the same cases by different authors.

At the Montefiore Hospital there were two cases in approximately 1,750 autopsies. However, four cases of carcinoma arising possibly in the ampulla of Vater can be found in the files; but they were not considered as primary duodenal tumors.

TABLE I

Frequency of Primary Duodenal Carcinoma in General Autopsies

	Necropsies	Duodenal Ca.	Percentage
Perry and Shaw	17,652	4	.020
Fenwick and Fenwick	19,518	18	.090
Maydl	20,480	5	.010
Nothnagel	21,358	5	.020
Zelman	21,624	3	.013
Muller	5,621	6	.100
Deaver and Ravdin	151,201	50	.033
Schlesinger	42,000	7	.017
Rupp	4,258	1	.023
Tiemann	3,350	2	.060
Geiser	11,314	7	.062
Meyer and Rosenberg	10,876	4	.037
Jefferson	109,201	43	.039
Brill	41,838	7	.016
Howard	1,654	3	.182
Montefiore Hospital	1,750	2	.114
	483,695	167	.035%

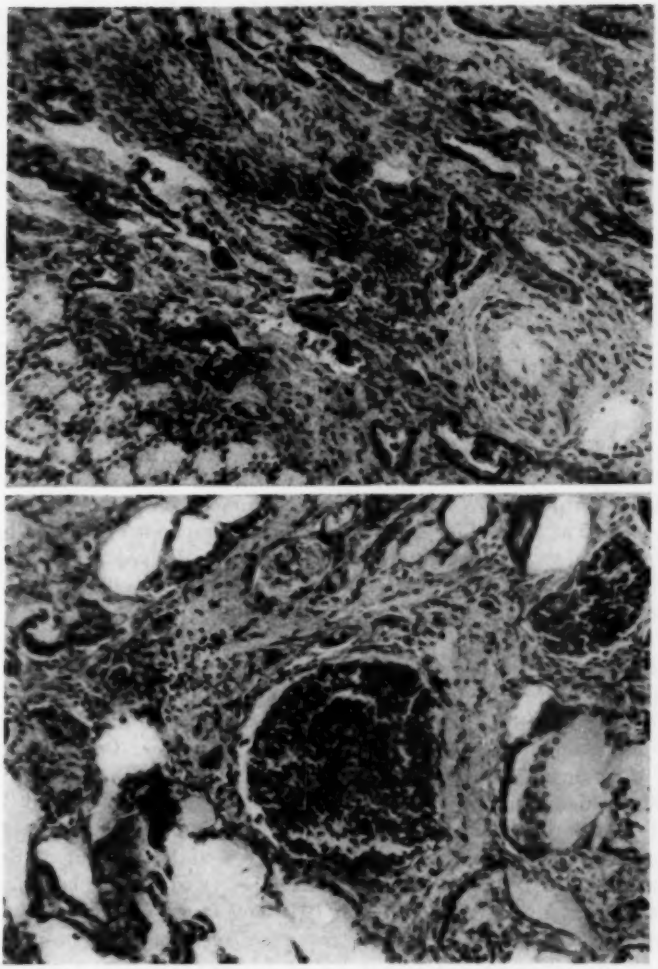

FIG. 3. (*above*) H. & E. × 100. Case 2 showing, in the upper left hand corner, normal Brunner's gland with gradual transition to atypical glands lined by hyperchromatic nucleated cells and mitotic figures. (*below*) H. & E. × 400. Showing, besides the glands, some nests of pleomorphic epithelial cells, poorly differentiated.

The next table illustrates the frequency with which primary carcinoma of the duodenum occurs in comparison with that of the jejunum and ileum combined, and shows that the duodenum is affected in approximately 45 per cent of the cases of primary carcinoma of the small intestine. This indicates that the duodenum is the site of malignant process almost as frequently as the other two divisions of the small intestine combined.

TABLE II

Frequency of Primary Duodenal Carcinoma Compared with Primary Jejuno-Ileal Carcinoma

	Small Intestinal Carcinoma	Duodenal	Jejuno-Ileal
Deaver and Ravdin	132	69	69
Mayo Clinic	39	15	24
Brill	30	15	15
Aaron	17	7	10
Meyer and Rosenberg	10	4	6
Nickerson	8	6	2
Medinger	16	3	13
Madyl	6	2	4
Nothnagel	11	5	6
Raiford	12	5	7
Stein	6	2	4
Howard	6	3	3
Total and percentage	293	130 (45%)	163 (55%)

It has been reported that 3 per cent of intestinal carcinomas are found in the small bowel.

Primary duodenal carcinoma is anatomically subdivided into suprapapillary, peripapillary, and infrapapillary tumors on embryologic, pathologic, as well as upon clinical grounds. The suprapapillary portion is above the common duct opening into the duodenum; it is derived from the foregut. The infrapapillary portion arises from the mid-gut (yolk sac) while the region of the papilla is in the zone between the two.

The literature dealing with all three groups was very carefully analyzed in a series of articles by Stewart and Lieber [1, 2] up to 1937 for supra- and infrapapillary growths and up to 1939 for peripapillary tumors. These three papers reviewed a total of 565 previously reported cases of which only 298 were acceptable as authentically proved. To these the authors added 25 of their own, making a total of 323 acceptable cases. In 1942, Berger and Koppelman [3] brought the statistics up to date when they found 80 additional cases in the literature of which 62 were acceptable. Adding the single case which they reported, the aggregate figure of authentic primary duodenal carcinoma up to 1942 was 386. We have reviewed the available literature on the subject since that time up to 1948 and found 72 cases of which 67 proved acceptable. By adding our two cases reported, the total number of cases up to 1948 is 453. Of these 102 or 22.5 per cent were suprapapillary; 268 or 59.2 per cent were peripapillary; and 83 or 18.3 per cent were infrapapillary. However, 15 of the cases reported as acceptable in our studies have been previously reported, reducing the total number of reported cases to 438.

Table 3 shows that, of the anatomic division of the duodenum, the second portion undergoes malignant degeneration far more frequently than the other parts. However, the Vaterian ampulla not infrequently gives rise to malignancies which must be classified as tumors of the pancreatic and biliary

systems and not as true primary tumors of the duodenum. The difficulty in making this distinction undoubtedly has accounted in part for the high percentage of primary carcinomas reported in this portion of the duodenum. The first portion of the duodenum ranks second in order of frequency. Whether or not carcinoma may arise from a duodenal ulcer is a much debated question and will be discussed later. The third portion is the part least frequently involved; only 18.3 per cent of the total number of duodenal cancers have been in this segment.

TABLE III

Distribution of Primary Duodenal Carcinoma

	Cases Analyzed	Cases Acceptable	Supra-papillary	Peri-papillary	Infra-papillary
Stewart and Lieber (1937)	590	323	63	222	38
Berger and Koppelman (1942)	81	63	14	29	20
–1948	72	67	25	17	25
Total	743	453	102	268	83
Percentage			22.5%	59.2%	18.3%

ETIOLOGY

Carcinoma of the duodenum occurs in late middle and advanced life, the average age being 52 to 55 years. It is more frequent in men than in women, a ratio of 2.5 or 3 to 1. Up to the present time no more is known concerning the true cause of duodenal carcinoma than of malignant processes in any other part of the body. However, many theories have been advanced. Geiser [4] suggested that chronic irritation caused by the duodenal contents on the mucosal folds was an important factor. He also suggested that in the area contiguous to the papilla of Vater, there is a conflict of two types of epithelial cells, with a resultant proclivity to carcinomatous degeneration. This he advanced to explain the greater frequency of carcinoma in the second portion of the duodenum.

Predisposed factors based on the anatomic relations of the duodenum have for many years been noted. These include the fixation of the duodenum by the parietal peritoneum, the four flexures, the difficulty in adapting itself to its contents as well as the trauma that was incident to it in its normal relation over the third lumbar vertebra. Likewise, the duodenum is said to be the most dilated portion of the small intestine and thence favorable for stasis and consequent irritation. The irritation incurred by the projecting papilla has also received consideration. The causal relation of the ulcer to carcinoma has long been debated. Jefferson [5] stated that the "causal relation of the simple ulcer to carcinoma is difficult to establish." It is common knowledge that 99.2 per cent duodenal ulcers occur in the first portion of the duodenum. This in no way can be correlated to the position and incidence of duodenal carcinoma. According to Lichty, the incidence of carcinoma arising on duodenal ulcers is 1/80 while that of gastric carcinoma

developing from gastric ulcers is 1/25. Malignant degeneration of polyps and adenomas has been advanced as another theory. It is true that these are the most common benign tumors in the small intestine. However, it has been stated by Raiford [6] that the highest incidence of this benign tumor is in the ileum. Further we must admit that carcinomas of the duodenum and small intestine are not frequently associated with polyposis.

Some have claimed that Brunner's gland found in the first few inches of the duodenum and the tissue surrounding the papilla of Vater may at times undergo a malignant degeneration. Robertson [7] claims that this rarely, if ever, occurs, and that proliferation at these sites gives a questionable type of malignancy. The old theory of malignant degeneration of heterotopic or aberrant gastric or pancreatic tissue has been suggested with regards to carcinoma of the duodenum. Aberrant pancreatic islands have been found in 23.5 per cent of all duodenums. The incidence of diverticuli with or without ectopic pancreatic or gastric mucosa is notable. As suggested by Raiford,[6] the small intestine develops during the last four months of fetal life and therefore there is less opportunity for arrested development and misplaced embryonic tissue. We are prone to agree with Dixon [8] et al., who are of the opinion that in spite of all these elaborate theories, carcinoma of the duodenum originates in the main from anaplastic changes in the duodenal mucosa itself but may occur from any of the aberrant tissues mentioned above which may be present.

Pathology

Carcinoma of the duodenum is most often primary in origin. It is thought to arise from the mucosa, Brunner's glands, aberrant pancreatic or gastric tissue. In commenting on the latter, Bland-Sutton [9] has remarked that any theories indicating aberrant pancreatic tissue or Brunner's glands "belong to the domain of fiction."

By far the most frequent type of duodenal carcinoma is the cylindrical cell adenocarcinoma arising from the intestinal mucosa and having a tendency to encircle the duodenal lumen. Some of them are spheroidal cell adenocarcinomas and a few cases of the squamous and adenosquamous variety have been reported. Dixon [8] in a series of 44 cases found three to have a concomitant ulcer and one aberrant pancreatic tissue. Stenosing and polypoid lesions are most common. These infiltrate, ulcerate, and tend to encircle the lumen often causing intestinal obstruction. Carcinomas have been classified on the basis of the fibrous tissue reaction as scirrhous, medullary, and colloid. The differentiation between primary duodenal carcinoma and carcinoma of the papilla is often quite subtle. It has been noted by Pic [10] that carcinoma of the papilla constituted circumscribed tumors occupying only a portion of the wall whereas true duodenal carcinoma develops in an annular or cylindric manner to encircle the entire circumference of the lumen. Metastases occur infrequently and when they do occur, they are late and

usually involve the regional lymph nodes, mesentery, liver, and lungs. Less often the peritoneum, bone, and supraclavicular nodes are involved.

Discussion

The diagnosis of a primary malignant condition of the duodenum is one of the most difficult problems confronted in medicine. There are two outstanding reasons why the diagnosis of carcinoma of the duodenum is rarely made. On the one hand, there is a lack of characteristic symptoms and signs with an abundance of features common to several other lesions of the upper part of the abdomen; on the other hand, its rarity results in the frequent failure to include it in the differential diagnosis.

Consequently, in only a few cases recorded in the literature has the diagnosis even been suspected. Hence, most cases were diagnosed at operation or at autopsy. Some writers claim that the diagnosis is practically impossible clinically. There are several important steps leading to a possible diagnosis of this condition which should be emphasized.

It is particularly important for us to realize that we are now passing through a phase in which the myth of the rarity of primary duodenal carcinoma is being exploded. At the Mayo Clinic 29.2 per cent were diagnosed clinically in 1940.[11] More recently Dixon [8] and his associates at the Mayo Clinic reported pre-operative diagnosis of 35 cases in a series totaling 37. In addition, their report of 49 cases certainly indicates that this lesion is not as infrequent as formerly supposed. The symptoms are varied and nonspecific. They are more easily understood if we correlate them to the pathologic process rather than the position of the lesion. The majority of cases complain of vague epigastric distress, some slight pain, anorexia, weakness, and weight loss. Nausea and vomiting are not infrequent. Anemia of the hypochromic type may vary in degree from moderate to marked. Jaundice is a late symptom and it may be intermittent. Occasionally massive hemorrhage is the initial symptom as it was in one of our cases. With this hematemesis and melena may occur. If we analyze these symptoms, we will observe that they can fall into four groups: (1) *Obstructive type.* The epigastric distress, anorexia, weight loss, gaseous eructations, nausea, and vomiting can readily be explained by an obstructive lesion, which may at times with transient edema, become totally obstructive. (2) *Ulceration.* Ulceration of the malignant lesion with subsequent bleeding and anemia will produce weakness and fatigue. The anemia of duodenal carcinoma is worthy of some note. The anemia may be macrocytic or microcytic. More frequently it is microcytic hypochromic due to chronic blood loss. With the bleeding, hematemesis and melena may occur. It should be remembered that as Dixon has pointed out, hematopoiesis following duodenal resection is not changed. (3) *Penetration.* The posterior penetration of an ulcerated malignant lesion will cause the typical gnawing pain occurring several hours after meals and unrelieved by food or alkali. This

exemplifies the type of pain in our first case. (4) *Obstruction of the biliary tract.* Jaundice, of course, is a frequent symptom, most notable in lesions of the second portion of the duodenum. This is frequently a terminal symptom. Intermittent jaundice is an earlier symptom and is probably due to a transient edema or necrosis with transient blockage of the ampulla. It still is true that jaundice occurs most frequently with lesions of the second portion of the duodenum. Diarrhea occurs but rarely due to the obstruction of the pancreatic duct. Gastric analysis reveals an achlorhydria in over 50 per cent of the cases. The gall-bladder is rarely palpable.

Roentgenography is the important procedure in the establishment of the diagnosis. It is to be noted that in both our cases diverticuli of the duodenum were erroneously reported by the radiologist. We must approach the diagnosis of duodenal diverticuli in patients of the carcinoma age with trepidation and not without scepticism ever mindful of the increasing incidence of duodenal carcinoma. Extraduodenal lesions causing extrinsic pressure defects and those lesions with complete obstruction of the duodenum cause the radiologist the greatest trouble in establishing a definite diagnosis. Although it was not used in our cases, duodenal intubation and drainage may be another aid to diagnosis in a suspected case of duodenal carcinoma. In the differential diagnosis, a malignancy of the pylorus and in the first portion of the duodenum must be distinguished. If roentgen-ray fails to demonstrate any gastric lesions but shows duodenal dilatation, this is good reason for excluding the stomach as the site of the disease. Free HCl is said to disappear earlier in cases of malignancy of the stomach than those of the duodenum. In the suprapapillary type, the abrupt onset of symptoms is a common occurrence and has been stated to occur in about half the cases, whereas symptoms of carcinoma of the stomach always develop slowly.

The peripapillary type of duodenal carcinoma which is the most common form causes greater difficulty in diagnosis. However, several important clinical points should be considered in differentiating this from carcinoma of the head of the pancreas. 1. In duodenal malignancy, jaundice is frequently intermittent in the early stages. 2. Since malignant lesions frequently encircle the lumen of the bowel, obstruction and obstructive symptoms will usually precede, by some time, the onset of jaundice. 3. Roentgen-ray evidence is often of value. 4. Carcinoma of the periampullary region of the duodenum produces late and local metastases in contradistinction to the early metastases of carcinoma of the papilla and biliary tract. However, in many cases, diagnosis is possible only with exploratory laparotomy.

The infrapapillary type is marked by gastric dilatation and an associated presence of bile and pancreatic juices and trypsin in the gastric contents. Attacks of acute abdominal pain and severe vomiting are not uncommon. This type has to be differentiated chiefly from malignant obstruction of the proximal jejunum and the pylorus of the stomach. The roentgen-rays should be of value in differential diagnosis. Furthermore, free hydrochloric

acid is more likely to be present in the infrapapillary type of duodenal carcinoma than in carcinoma of the pylorus. In carcinoma of the pylorus there is usually no bile, trypsin, or pancreatic juice present in vomitus or stomach content.

It should be stressed that in vague lesions of the upper abdomen, exploratory laparotomy should be a more frequently employed procedure. This principle stems from the great recent strides in duodenal and pancreatic surgery.

Course and Treatment

The course of the disease is short. The average duration of life after onset of symptoms has been given as five to 19 months, death usually occurring from general debility. Notable among the causes of death is gross hemorrhage which was the immediate cause of death in our cases. Perforation and peritonitis are also not uncommon as terminal events.

Treatment medically is of little avail except to afford the patient relief of symptoms. Since metastases occur late, surgery may be of value even in well advanced cases. In the absence of metastases and complications, resection of the growth with secondary anastomosis has usually been done. In cases about the papilla in which the biliary and pancreatic ducts are involved, resection and reimplantation of the ducts are being performed with increasing frequency.

The surgical mortality varies from 17 to 22 per cent.[6, 12, 13] The most frequent causes of postoperative death are hemorrhage and shock, peritonitis, pancreatic fistulae, mesenteric thrombosis, and coronary occlusion.

Those patients recovering from pancreatic resection may show faulty fat digestion, requiring pancreatin to maintain weight.

Summary

Two cases of primary suprapapillary adenocarcinoma of the duodenum are presented. The literature on all types of primary duodenal carcinoma is summarized covering a total of 438 proved cases to date of which 22.5 per cent were suprapapillary; 59.2 per cent were peripapillary; and 18.3 per cent were infrapapillary. The incidence, etiology, pathology, symptomatology, and course of this condition are discussed.

Carcinoma of the duodenum does not appear to be as infrequent as formerly believed. Its diagnosis, especially by roentgen-ray methods, is far from impossible. Recent advances in the surgery of the pancreas, ampullary region and duodenum, have removed duodenal carcinoma from the category of inoperable conditions. It is of importance therefore that clinicians should be alert to the possibility of its presence.

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THE CLINICAL DIAGNOSIS OF PERIARTERITIS NODOSA: REPORT OF FOUR CASES*

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Interest in periarteritis nodosa has accompanied the increasing literature on this disease. Over 400 cases have been reported and various theories of its etiology have been propounded. The diagnosis, however, is still most frequently made post mortem.

The diagnoses in the four cases described in this report were made clinically: three were confirmed at autopsy and the fourth by biopsy. They were observed in a period of 11 months in 1942 and 1943 on the Medical Service of the Fourth General Hospital while stationed overseas. The clinical diagnosis was not made in any other cases among the first 35,000 admissions. The cases are reported in some detail because it is believed possible to make the diagnosis by clinical observation with a reasonable degree of precision.

Case 1. This patient, white, male, age 22, noticed pain in his right heel on April 17, 1942, followed in three days by pain in the legs and thighs and swelling of the left knee. He was admitted to another hospital on April 21 where a distended abdomen and a rubella-like rash were noted. Subcutaneous nodules came and went on the extremities and two weeks after admission edema of the face and gross hematuria appeared, there previously having been noted heavy traces of albumin in all urine specimens. Blood pressure was 155/95 mm. Hg; low grade fever up to 99.6° F. daily was present; blood urea nitrogen was 28 mg. per cent; urine was loaded with red blood cells and albumin; white blood cell count was 12,000 per cu. mm.; and hemoglobin was 62 per cent shortly before admission to this hospital on May 26, 1942.

Past history was noncontributory except for the presence of frequent sore throats up to the age of 14 years. Examination showed a very ill young white man with a puffy, pallid face, generalized pitting edema, fading purpuric lesions on the posterior surfaces of the lower legs, and a subcutaneous nodule 5 mm. in diameter on the left forearm. Mucous membranes were pale and tonsils were hypertrophied. There were dullness and distant breath sounds at both lung bases. The heart was normal; blood pressure was 195/105 mm. Hg. There was moderate ascites. Mild periarticular swellings of the elbows, wrists, and fingers were noted. Neurological examination was normal. Urinalysis showed a specific gravity of 1.017, 2 plus albumin, and gross hematuria. White blood cells numbered 10,800 per cu. mm. Red blood cell count was 3,980,000 per cu. mm. and hemoglobin estimation was 85 per cent. Three per cent eosinophiles were in the differential count. Nonprotein nitrogen content of the plasma was 33 mg. per cent and total plasma proteins were 6.5 gm. per cent.

The patient lived for *eight* weeks after admission. During the *first* week the anasarca increased; pains in the legs became extreme; numerous evanescent nodules appeared under the skin; fever up to 102° F. occurred daily; and the laboratory findings remained unchanged except for an increase in the anemia. By the *third* week numerous other signs and symptoms had appeared. The sensorium had become clouded; there was one day of precordial pain; the heart enlarged to the left and a

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precordial friction rub was heard; weakness and numbness of the hands appeared followed swiftly by left wrist drop and paralysis of the fingers, weakness of the right forearm and wasting of muscles of both forearms and hands; all tendon reflexes were abolished for a time but the knee jerks returned within two days; anesthesia from mid-forearm distally on the left occurred with hypesthesia over the same area on the right. Nonprotein nitrogen of the plasma rose to 89 mg. per cent. Fever was lower, up to 100° F. daily.

During the *fourth* and *fifth* weeks the patient appeared weaker, paler and more confused. Albuminuria was marked and urinary sediment was loaded with red and white blood cells and hyaline and granular casts. Hemoglobin dropped to 50 per cent. Nonprotein nitrogen rose to 105 mg. per cent. Electrocardiogram, previously normal, showed 0.5 mm. depression of the S–T segments in Leads I, II and IV, diphasic T-waves in Leads II and IV, and no changes in the QRS complexes. By the end of the *seventh* week his mental state was clearer. The left wrist drop improved but the hand became weaker and atrophy of both forearms increased. Peripheral edema was less. Hemoglobin dropped to 37 per cent. Total plasma proteins dropped to 3.6 gm. per cent and non-protein nitrogen of the plasma rose to 173 mg. per cent. Electrocardiogram showed further changes with S–T_1 becoming isoelectric, T_1 and T_4 becoming upright and the P–R interval increasing from 0.16 to 0.21 second. During the *last* week of life the patient was euphoric; the pericardial friction rub increased in intensity; and the blood pressure dropped to 140/90 mm. Hg. The entire right hand became paralyzed. There was only minimal fever for the three weeks before death. The nonprotein nitrogen of the plasma fell to 80 mg. per cent. On July 23, 1942, he became suddenly confused, respirations became labored; he vomited a large amount of blood, bloody diarrhea ensued; blood pressure fell to shock levels; and he died 15 hours after the first hematemesis.

During his hospital course he received a trial of sulfathiazole therapy for 10 days without apparent effect. The administration of digitalis failed to improve urinary output or edema. Three blood cultures were sterile. A biopsy of a skin nodule was accidentally lost.

Autopsy Findings: Lesions typical of periarteritis nodosa were found in the lungs, liver, spleen, pancreas, adrenals, kidneys, prostate, testes, stomach, brachial plexuses, skeletal muscles, brain, and lymph nodes. The smaller branches and twigs of the arteries were principally involved. All coats were affected and various states were seen, from an acute exudative process to complete healing. Eosinophiles were present in moderate numbers. Areas of necrosis of the vessel walls occurred and a few small aneurysms had formed. The healed lesion showed organized and recanalized thrombi, with occasional calcium deposits. The stomach was filled with 1,000 c.c. of clotted blood and on the lesser curvature 4 cm. proximal to the pylorus was a large punched-out ulcer with an eroded artery visible in its base. On section, this vessel showed the typical lesions. There were multiple anemic infarcts in the lungs, adrenals, kidneys, and testes. A subacute glomerulonephritis was present in addition to the arterial lesions. A severe fibrinous pericarditis was found. Bronchopneumonia, chronic passive hyperemia of the lungs, and bilateral pleural effusion were noted. Ascites of 1,000 c.c. of clear fluid was found. Acute follicular hyperplasia and chronic passive hyperemia of the spleen, acute generalized hyperplastic lymphadenitis, chronic cholecystitis, fatty degeneration of the aorta and a calcified tubercle of a hilar lymph node were among the remainder of the pathological findings.

Comment: The widespread lesions found at autopsy more than explain the clinical manifestations. The gastric ulcer is intimately associated with disease of the arteries in the gastric wall. The glomerulonephritis as well as the arterial renal lesions accounts for the uremia and urinary findings.

The pericarditis is not associated with vascular disease of the heart. The brachial plexuses showed healed arterial lesions. The clinical diagnosis in this case was suggested in the first week of observation but could not be confirmed until after death.

Case 2. This patient, white, male, age 34, was admitted to the hospital on June 16, 1942. Soreness of the leg muscles had been present for two weeks. For four days there had been some soreness about the elbows and in the neck muscles. Faintness and nausea occurred the day before admission. In the past he had had vague aching of his muscles for several years, never severe enough to require medical attention. There had been right maxillary sinusitis following a tooth extraction three years previously resulting in occasional right facial pain and nasal discharge.

Initial examination showed a young white man who appeared mildly ill. There was tenderness about the elbows, right wrist, and calves of the legs, with pain on motion of these parts. The heart showed a moderately loud apical systolic murmur and the blood pressure was 155/95 mm. Hg. The liver descended 3 cm. below the costal margin during inspiration. All reflexes were present. Urinalysis was normal. Hemoglobin was 84 per cent, red blood cell count 4,640,000 per cu. mm., white blood cell count 10,000 per cu. mm., and the smear showed 5 per cent eosinophiles. Sedimentation rate was 30 mm. per hour. Films of the chest and teeth were normal, and of the sinuses showed cloudiness of most of them and sclerotic bone about both frontal sinuses.

The patient lived for *10* weeks after admission. During this time there was daily low grade irregular fever, at times continuous and at times remittent, reaching its highest of 102° F. during the third week and again the day before death. During the *first two* weeks there was constant headache. Pains in the arms subsided but the leg muscles remained tender. White blood cells rose to 18,400 per cu. mm. In the *third* week generalized muscle wasting was noted and bilateral ulnar palsy rather suddenly appeared. Indigestion, constipation, and severe abdominal cramps began. Biopsy of the left gastrocnemius muscle failed to show any pathology. Lumbar puncture produced clear fluid containing 12 cells per cu. mm., 11 of which were lymphocytes, and 45 mg. per cent of protein. Cerebrospinal fluid Kline test was negative. During the *fourth* week neurological signs progressed, including sensory loss over the radial and ulnar distribution bilaterally, and over the distribution of the first sacral segment on the left foot. General wasting increased and the abdominal symptoms persisted with occasional vomiting.

In the *fifth* week hyperesthesia replaced anesthesia in the involved areas. There was some return of function of the right hand, but weakness of the left hand and of both legs increased. The abdominal symptoms abated somewhat and the blood pressure fluctuated between 170/100 and 120/80 mm. Hg. During the *sixth* and *seventh* weeks he became mentally confused and aphasia was noted for a 24 hour period. The motor powers of the hands returned slightly but bilateral foot drop developed and then rapidly improved. Urticaria appeared for four days and vomiting became more severe. Lumbar puncture now obtained clear fluid with 79 cells per cu. mm., 60 of which were lymphocytes, and 48 mg. per cent of protein. During the *eighth* week fluid at the base of the left lung appeared. The reflexes changed from day to day and muscle power of the hands and arms increased. Cell count in the spinal fluid dropped to 4 per cu. mm., and cultures were sterile. In the *ninth* week x-ray studies were made of the upper intestinal tract which showed a tremendously dilated stomach and duodenum down to its middle third, and the stomach seemed to be pushed forward by a mass. Frequent extrasystoles appeared and the electrocardiogram, previously normal, showed right axis deviation, isoelectric T-waves in the limb leads and diphasic T-waves in Lead IV. A nodule in the right testis was felt for the first time.

Blood counts showed no significant anemia but a leukocytosis of 26,000. Plasma proteins totaled 4.9 gm. per cent, and plasma chlorides as NaCl 505 mg. per cent. On August 19, 1942, laparotomy was performed and an inflammatory mass was found which was considered either to be in the pancreas or lesser peritoneal cavity. Jejunostomy was done, following which the patient lived for five days. Four plus albuminuria appeared two days before death. Peritoneal culture grew staphylococci, colon bacilli, and diphtheroids. The patient suddenly died following an involuntary stool on August 24, 1942.

Treatment included blood transfusions, gastric suction and large doses of vitamin B complex. Three blood cultures were sterile.

Autopsy Findings: Vascular lesions typical of periarteritis nodosa were found in the heart, lungs, liver, spleen, pancreas, adrenals, kidneys, prostate, testes, stomach, intestines, brachial plexuses, and the Circle of Willis. There were multiple small infarcts in the organs, gross nodular lesions in the branches and twigs of arteries, and a typical histological appearance except for the absence of tissue eosinophilia. The lesions in the arteries were mostly of the healed type. Nodules were visible in the small branches of the coronary arteries, chiefly of the circumflex branch of the left coronary. In the myocardium of the left ventricle there were numerous small infarcts in the distribution of the deep bulbo-spiral and sino-spiral muscles which could be seen grossly.

There was a generalized peritonitis with fetid yellowish brown exudate and a large abscess in the omental bursa. The latter was caused by a large perforating peptic ulcer on the posterior aspect of the stomach 1.5 cm. proximal to the pylorus. On microscopic section this was an acute ulcer and the vessels of the stomach were extensively involved with the lesions of periarteritis nodosa. The remainder of the findings included bilateral bronchopneumonia, compression atelectasis of the lower lobes of both lungs and a recent jejunostomy.

Comment: Again the lesions of periarteritis nodosa are widespread and explain the clinical findings. The gastric ulcer is associated with the vascular lesions in the stomach wall and indirectly produced death by perforation and peritonitis. The arterial lesions in the left ventricle account for the electrocardiographic changes. The small amount of skeletal muscle examined showed no disease. The nutrient arteries of the brachial plexuses were extensively involved. The clinical diagnosis in this case was suggested after the neurological changes began to appear, to explain them as well as the hypertension, leukocytosis, and fever. The abdominal findings were difficult to correlate with periarteritis nodosa until autopsy. The confusing picture stimulated various members of the hospital staff to record no less than 17 opinions as to the cause and mechanism of this man's illness.

Case 3. This patient, age 36, white, male, first noticed pains in his legs about July 1, 1942. Following this, weakness, nausea with occasional vomiting and weight loss progressed insidiously until August 12, 1942, when he was admitted to another hospital. For the next two months he was observed to have daily low grade fever with persistence of all symptoms and a one-week period of pains in the arms. He lost 15 pounds of weight and the diagnosis of arthritis of undetermined cause was made. On October 2, 1942, he was admitted to this hospital.

The past history was noncontributory. Examination showed a chronically ill young white man. The temperature was 100° F. The heart and lungs were normal, and the blood pressure was 140/100 mm. Hg. The liver was palpable and somewhat tender. Pressure over the maxillary sinuses produced some pain. There was gen-

eralized muscle tenderness, especially marked in the gastrocnemii and biceps. Weakness of the trunk muscles, biceps, and extensors of the wrists was noted. Neurological examination revealed all the deep tendon and superficial reflexes to be absent, except for a hypoactive right knee jerk. Sensory examination was normal.

Admission urinalysis showed a trace of albumin and 2 to 10 white blood cells per high power field. Hemoglobin was 85 per cent, and red blood cells numbered 4,900,000 per cu. mm. Differential white blood cell count fell within the normal ranges, eosinophiles being 1 per cent. Sedimentation rate was 34 mm. per hour. Blood urea nitrogen was 16 mg. per cent. The blood Kahn and agglutination with *B. abortus* were negative. Plasma proteins totaled 6 gm. per cent. Stool and sputum examinations were negative. Blood cultures were sterile. One positive culture for *Streptococcus lactis fecalis* was obtained from the urine. Cerebrospinal fluid examination showed 9 cells, 8 of them being lymphocytes, a negative Kahn, 27 mg. per cent of protein, and a gold curve of 1112100000. Fluoroscopy and films of the gastrointestinal tract were reported as negative.

During the *first* week in the hospital there was no change and fever ranged up to 101° F. daily. During the *second* week the temperature became normal, and much of the muscle pain and tenderness disappeared. A small subcutaneous nodule on the left ankle appeared, was slightly tender, and disappeared in 24 hours. The liver was no longer palpable, and blood pressure dropped to 130/78 mm. Hg. Hypesthesia on the posterior surface of the left thigh was noted at this time. During the *third* week abdominal symptoms recurred, with indigestion, epigastric pain and vomiting, and the liver again became palpable. Blood pressure was 134/90 mm. Hg and daily fever to 100° F. recurred. Various tendon reflexes were found to be present intermittently. From the *fourth* to the *ninth* weeks in the hospital he felt fairly well except for weakness. Small nodules were noticed to come and go on the hypothenar eminences. During the latter part of this period he was ambulatory, appetite improved but a sense of well-being did not return. The hemoglobin dropped to 65 per cent and the red blood cell count fell to 3,300,000 per cu. mm. Nine per cent eosinophilia was noted. The urine persistently showed 2 to 3 plus albumin, and many red blood cells appeared in the sediment. The plasma proteins were 7.2 gm. per cent with an albumin-globulin ratio of 0.9.

During the *ninth* to the *eleventh* weeks he seemed to be slowly improving. No real paralysis or anesthesia was found. The reflexes were changeable though usually absent. Transient urticaria appeared once. On December 14, 1942, biopsy of the left gastrocnemius muscle was performed. Treatment during his stay consisted of thiamin chloride, liver extract injections, a 10 day course of sulfathiazole administration and one blood transfusion. He was transferred to the United States on December 18, 1942.

Biopsy report (gastrocnemius muscle): Grossly, the muscle appeared normal. Microscopically there were numerous lesions typical of periarteritis nodosa, involving the small arteries. In some arteries the entire diameter was involved whereas in others only a quarter or half of the diameter was involved. There were degeneration and necrosis of all coats with considerable cellular exudate consisting of lymphocytes, small mononuclear cells, and small numbers of eosinophiles. In a few areas the entire thickness of the media was necrotic with the formation of a false aneurysm. The muscle fibers showed degenerative changes and focal accumulation of lymphocytes.

Comment: Unfortunately this case was not followed after leaving the hospital. It is known that he died about six months later, making the duration of his illness a little less than a year, but symptoms subsequent to December, 1942, and cause of death are unknown. The diagnosis was suspected because of the fever, hypertension, urinary findings, and neuromuscular

symptoms; and was proved by muscle biopsy. There was a partial remission of symptoms when last observed.

Case 4. This patient, age 25, white, male, was first admitted to this hospital on January 9, 1943. He had tertian malaria and was appropriately treated. On February 16 he seemed well and had no complaints. However, his blood smear was again positive for *P. vivax* and treatment was reinstituted.

On February 19, 1943, he had an upper respiratory tract infection with pharyngitis and right catarrhal otitis media. The temperature on that day was 99.8° F. and for the following week showed a daily step-like rise to a maximum of 103° F. He lived for 10 weeks after the onset of his fever. Diffuse abdominal pain and generalized muscular pain and tenderness came on with the fever, to the point where he was unable to walk. Repeated malarial smears were negative, and there was no fall in temperature with intravenous quinine administration. Examination at this time showed a systolic murmur at the aortic area which had not previously been present. The abdomen was distended and diffusely tender, most marked in the right upper quadrant. Neurological examination was normal except for absent ankle jerks. Laboratory findings during the *first* week were as follows: white blood cell count 21,150 per cu. mm.; hemoglobin 95 per cent; 82 per cent polymorphonuclear cells in the blood smear; 2 plus albuminuria with 4 to 7 white blood cells and an occasional red blood cell per high power field of centrifuged urinary sediment; blood urea nitrogen 15 mg. per cent; total plasma proteins 7 gm. per cent with an albumin-globulin ratio of 0.8; icteric index 7; two negative blood cultures; normal electrocardiogram except for a tachycardia of 125; normal chest film; marked distention of both large and small bowel was seen on a flat film of the abdomen.

During the *second* week general muscular wasting began and all deep tendon reflexes disappeared. The patient became weaker and more irritable with short periods of delirium. Fever was unremitting with an average level of 101° F. Faint icterus appeared, combined with an increasing pallor. Blood pressure, which had been 130/80 on admission, rose to 178/118 mm. Hg at the end of the second week. Marked tachycardia persisted. Muscle tenderness became less marked and concurrently all deep tendon reflexes returned except for the ankle jerks. Biopsy of the left soleus muscle at a point where there had been marked tenderness showed no vascular disease. Hemoglobin dropped to 80 per cent, and white blood cell count rose to 30,700 per cu. mm. Lumbar puncture produced a clear fluid containing no cells, 25 mg. per cent of protein, 66 mg. per cent of glucose and 647 mg. per cent of chlorides as NaCl. Spinal fluid Kahn test was negative and the gold curve was 0012200000. Mild albuminuria persisted.

During the *third* week the slight icterus faded. Left foot drop developed and ankle jerks, triceps jerks and abdominal reflexes were absent. Tachycardia and hypertension up to 180/118 persisted. The heart seemed slightly enlarged to the left and râles appeared at both lung bases. During the *fourth* week temperature was unremitting at a level of 100 to 101° F. Blood urea nitrogen rose to 26 mg. per cent. Electrocardiogram showed an upright T_3 which had previously been slightly inverted.

From the *fifth* to the *tenth* weeks the course was slowly downward. Fever was not present for only seven days of this time. Mental confusion was present for short periods. Muscular wasting slowly progressed and the foot drop persisted. The deep tendon reflexes came and went in a capricious manner. At no time could sensory changes be demonstrated. Gallop rhythm developed as the heart seemed to enlarge slightly beyond the mid-clavicular line. Râles persisted at the lung bases. The right upper quadrant tenderness never disappeared, although most of the pain and distention subsided. Retention of urine developed, requiring an indwelling catheter. Blood pressure remained elevated at the level of 170/120 mm. Hg until just before death.

Leukocytosis and neutrophilia persisted but eosinophilia was never noted. Hemoglobin dropped to 63 per cent. Blood urea nitrogen rose to 56 mg. per cent. Chest film in the last week showed some enlargement of the heart shadow with mottling of the distal two-thirds of both lung fields. Electrocardiograms showed only digitalis effect. On April 10, 1943, he suddenly complained of near-blindness in the right eye. Ophthalmoscopic examination showed bilateral retinal edema most marked in the region of the maculae and optic discs. The arteries were tortuous and the veins distended. There were occasional small flame-shaped hemorrhages and poorly defined grayish-white exudates in both retinae. The central field of vision in the right eye was poorly outlined. The ophthalmologist considered this to be a local vascular lesion of the papillomacular bundle of the right optic nerve.

On April 15, 1943, temperature rose somewhat and *P. vivax* again appeared in the blood smear. Another blood culture was sterile. On May 1, 1943, after he had lapsed into coma the day before, his blood pressure fell to 70/38 mm. Hg; there was marked muffling of the heart sounds and respirations ceased. Treatment had consisted of antimalarial therapy, transfusions, a course of sulfathiazole to which he became sensitive, and digitalis for the last four weeks of his illness.

Autopsy Findings: Lesions typical of periarteritis nodosa were found in the heart, aorta, liver, spleen, pancreas, adrenals, kidneys, testes, epididymes, alimentary tract, brachial and sacral plexuses, and the celiac axis and its branches. The small branch arteries, 1 to 2 mm. in diameter, were chiefly affected and the lesions were mostly of a long-standing or "healed" nature. No polymorphonuclear or eosinophilic leukocytes were encountered in the exudation, and a few areas of fibrinoid or hyalin necrosis were encountered. The veins were involved in the kidneys and lungs. The principal cardiac lesion was marked diffuse fatty degeneration with scattered foci of periarteritis nodosa. The liver showed acute diffuse necrosis and chronic cholangitis with bile casts in greatly dilated intrahepatic bile ducts but no disease of the extrahepatic bile duct system. The kidneys showed subacute focal glomerulonephritis in addition to the arterial lesions. A subacute penetrating ulcer of the posterior aspect of the second portion of the duodenum was found, beneath which the pancreatico-duodenal artery was thrombosed. Sections of the spinal cord showed scattered small foci of demyelinization of the gray matter, especially marked in the lateral and posterior columns. The remainder of the findings included bronchopneumonia of all lobes, acute fibrinous pleurisy, subacute gastritis and duodenitis, and a ganglioneuroma of the right adrenal gland.

Comment: Again the disease is widespread and accounts for the major portion of the clinical picture. Nutrient arteries of nerves were involved in the brachial and sacral plexuses. Fatty degeneration of the myocardium, necrosis of the liver and glomerulonephritis accompany the arterial lesions. Ulceration of the duodenum is in association with the vascular lesions in its wall. The clinical diagnosis was suggested during the initial period of high fever when the blood pressure rose and the urinary and neurological changes appeared. The muscle biopsy failed to support the clinical impression.

Discussion

The etiology of periarteritis nodosa is unknown and theories include an unknown specific infection, an allergic reaction of the arterial system occurring in the course of various infections and toxemias, or that it is closely related to rheumatic fever.[11] The frequency with which infection

precedes the onset of the disease has been emphasized [2, 9, 19] and may bear a causal relationship. The recent experiments of Rich and Gregory [18] and Rich's autopsy material [16, 17] strongly suggest that the disease is a manifestation of the anaphylactic type of hypersensitivity. The pathology of the disease is a necrotizing arteritis or a hyaline or fibrinoid necrosis of the arterial wall together with a surrounding inflammatory reaction. These lesions vary in severity, number, and distribution, and lead to aneurysmal dilatations of the arteries and to degenerations, infarcts, necroses, ulcerations, inflammations, fibroses, and hemorrhages occurring in different organs [11] and explain the protean clinical manifestations. The organs most often involved are the kidneys, heart, liver, gastrointestinal tract, mesenteric vessels, muscles, spleen, lungs, and the central and peripheral nervous system.[13]

There have been numerous recent reviews and case reports of this disease [1-15, 19] with tabulation of large numbers of clinical symptoms and signs. In 177 cases [15] the list of clinical findings considered to be of enough importance to mention totals no less than 43 (table 1).

TABLE I

Symptoms of Periarteritis Nodosa, 177 Cases, Modified after Logue and Mullins

Fever	81%	Muscle soreness	26%
Leukocytosis	73%	Visual disturbances	23%
Albuminuria	65%	Nodules	23%
Abdominal pain	56%	Nausea	21%
Hypertension	53%	History of allergy	21%
Edema	49%	Coma	21%
Neuritis	49%	Atrophy	20%
Hematuria	48%	Cyanosis	20%
Anemia	48%	Hematemesis or bloody stools	18%
Tachycardia	48%	Pain in chest or pressure	17%
Rapid onset	45%	Uremia	13%
Weakness	45%	Icterus	12%
Loss of weight	44%	Convulsions	11%
Dyspnea	40%	Adenopathy	11%
Cough	36%	Positive serologic reaction	8%
Emaciation	34%	Chills	8%
Sensory involvement	34%	Diarrhea	6%
Arthritis	34%	Vertigo	5%
Vomiting	33%	Other skin eruption in absence of purpura	4%
Eosinophilia (4% plus)	33%	Hemoptysis	1%
Purpura or petechiae	27%		
Headache	26%		
Central nervous system involvement	26%		

It would seem obvious that there is no workable group of clinical findings from which a diagnosis can easily be made. Leischman [14] assembled 15 fundamental signs of diagnostic value. He believes that the basic clinical picture is that of "a severe, progressive toxemia characterized by fever, muscular asthenia, loss of weight and anemia" and that all other signs can be ascribed to local arterial lesions.

The signs and symptoms in our four cases indicating involvement of the organs or systems are tabulated in table 2. The general or non-specific symptoms of the disease which occurred in our cases are shown in table 3 and in large part agree with those in previous reports.

TABLE II

Organs and Systems Involved Clinically	Number of Cases	Signs and Symptoms Indicating Involvement
Musculature	4	Pain, tenderness, wasting, asthenia.
Kidneys	4	Edema, hematuria, albuminuria, cylindruria, azotemia, hypertension.
Gastrointestinal tract	4	Abdominal distention, hemorrhage, nausea, pain, duodenal obstruction, omental bursa abscess.
Peripheral nerves	4	Sensory disturbances, paresis, paralysis.
Heart	3	Edema, precordial pain, dyspnea, pericardial friction rub, cardiac enlargement, electrocardiographic changes, cardiac murmurs, unusual tachycardia.
Liver	3	Hypoproteinemia, hepatomegaly, jaundice.
Central nervous system	3	Delirium, headache, pleocytosis.
Skin and subcutaneous tissue	3	Macular or purpuric rash, nodules, urticaria.
Lungs	2	Cough, parenchymal râles.
Joints	1	Swelling, pain, tenderness.
Eyes	1	Amblyopia, retinal edema, central scotoma, retinal hemorrhages, and exudates.
Testicle	1	Palpable nodule.

Periarteritis nodosa may be confused with any prolonged febrile illness such as typhoid fever, miliary tuberculosis, subacute bacterial endocarditis, trichiniasis, disseminated lupus erythematosus, and the like. It may also be confused with disease of various organs if the arterial lesions predominate locally in one organ or system. As in Case 2, where 17 opinions are listed in the hospital record, many diagnoses are frequently offered in the consideration of an individual case. It is this discrepancy between manifestations and possible diagnoses which is the one clinical characteristic of the disease.[12, 14, 19]

TABLE III

Nonspecific or Constitutional Manifestations

	Number of Cases
Fever	4
Weakness and malaise	4
Weight loss	4
Hypertension	4
Anemia	4
Leukocytosis	3
Headache	3
Preceding infection	1
Eosinophilia	1

Periarteritis nodosa should be considered whenever the clinician is confronted by an illness characterized by fever, weight loss, malaise, and weakness; which looks like a chronic or subacute infection although its nature cannot be found; and which presents a confusing picture of clinical signs pointing to diseases of organs or systems which are uncommonly seen together; for example, neuritis and nephritis, heart failure and subcutaneous nodules, rheumatic fever and hepatitis. In a few cases general symptoms are minimal or absent [11] and the local manifestations reflect the arterial dis-

ease. However, even in these difficult problems as time progresses other more widespread symptoms are apt to occur. If the disturbances in any one organ can be attributed to vascular disturbances such as hematuria, Raynaud's phenomenon or electrocardiographic changes, then an attempt can be made to explain distant and seemingly unrelated symptoms on a similar basis.

Summary

Four proved cases of periarteritis nodosa in which the diagnosis was made clinically are described, and the fundamental picture of a sick individual with fever, malaise, weight loss, and asthenia is emphasized. Add to this picture, which occurs commonly in all debilitating illnesses, the *absence* of evidence of known infectious, parasitic, neoplastic, congenital or metabolic diseases, and the *presence* of evidence of involvement of usually more than one organ or system, and periarteritis nodosa must be seriously considered. Biopsy of muscle, cutaneous nodule or intra-abdominal organ is the only positive way of making the diagnosis during life, but a strong clinical suspicion can be aroused when the diversity of the manifestations of periarteritis nodosa is considered and applied to the problem at hand.

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SUSTAINED ANURIA IN LOWER NEPHRON NEPHROSIS: REPORT OF TWO CASES TREATED CONSERVATIVELY WITH RECOVERY *

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It is the purpose of this paper to report two cases of lower nephron nephrosis with sustained anuria who recovered following conservative therapy alone. These two cases are considered to be of more than usual interest because of the long duration of the anuria—10 days in one case and 11 days in the other—yet recovery ensued. According to Kugel,[18] tubular regeneration in acute toxic nephrosis begins on the third day after injury, and is complete on the fourteenth. This author states that spontaneous diuresis in acute toxic nephrosis usually occurs by the eleventh or twelfth day. These two cases illustrate the fact that man can live anuric for 10 and 11 days without the use of artificial methods to remove urea and toxic products from the blood; since diuresis usually occurs spontaneously by the eleventh or twelfth days, it would seem that some question could be raised as to the need for such methods as peritoneal lavage or artificial kidney in the treatment of the anuria of lower nephron nephrosis. The term "anuria" in this paper is not used in its strict literal sense, but as indicating a urinary output of less than 100 c.c. per 24 hours—a commonly used interpretation.

Case Reports

Case 1. A 43-year-old white male refrigerator mechanic was admitted to the Cincinnati General Hospital for the first time on December 13, 1947.

History: For four months preceding admission, the patient had used carbon tetrachloride in cleaning refrigerator parts for half an hour or so once or twice weekly. A week prior to admission, he began to consume large quantities of alcoholic beverages. The day before he became ill, he worked all day in a closed room, 32 by 64 feet, using carbon tetrachloride to clean refrigerator parts. There was in this same room an open pan of carbon tetrachloride the entire day. That night, the patient did not feel well. He drank a few bottles of beer and took one drink of whiskey, following which he vomited. The next morning, he developed a constant aching epigastric pain accompanied by persistent vomiting. Oliguria and dark urine were noted this same day. The patient came to the hospital late that same night and was admitted. Past history revealed mild chronic alcoholism and an attack of severe right upper quadrant pain three weeks prior to admission; this pain had required morphine for relief.

Physical examination: On admission, temperature, pulse, and respirations were normal. The only positive physical findings were a blood pressure of 135/80 and a large tender liver felt three fingers'-breadth below the right costal margin.

Laboratory data on admission: Hemoglobin 17 gm.; red blood cells, 5,230,000; white blood cells, 12,200; 85 per cent polynuclears, 13 per cent lymphocytes, 1 per cent

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eosinophiles, and 1 per cent basophiles. Urine: pH 4.5; albumin, 3 plus; loaded with white blood cells, positive for bile. Kahn test negative. Blood urea nitrogen, 16 mg. per 100 c.c. of blood. CO_2 combining power 44 volumes per cent. Blood chloride 528 mg. per 100 c.c. of blood. Serum amylase 91 units. Chest x-ray: heart of normal size; lung fields clear.

Course: See table 1 for summary. The patient was virtually anuric for the first 10 hospital days. Because of this, an attempt was made to restrict fluids to the output plus 1,000 c.c.; this attempt was not always successful, as may be seen in the table. Because of persistent vomiting, most feeding was done parenterally.

TABLE I

Case 1, 43-Year-Old White Male

Hosp. Day	1	2	3	4	5	6	7	8	9
BUN	16	30			95	100	110	115	135
CO_2	44				44		49	42	41
Chloride	528				436	419	426	466	452
Intake, c.c.	Outside	?	1000	2600	4550	1900	2575	975	550
Urine output, c.c.	Outside	Prob. none	Prob. none	5	10	0	30	40	55
B.P.	135/80				160/85	145/80			180/100
Weight, pounds								146	145½

Hosp. Day	10	11	12	13	14	15	16	17
BUN	150	130	140	170	120	120	158	140
CO_2	43	36	33	30.4	28		46	36
Chloride	463	440	455	424	439	456	483	502
Intake, c.c.	1050	715	795	2875	1195 plus	1950	1350	3610
Urine output, c.c.	105	225	325	720	1350	1950	2600	2750
B.P.	155/90	170/80	160/80	155/80				135/85
Weight, pounds			143		144	137	134	

Hosp. Day	18	19	20	21	22	24	27	29	42	43
BUN	99	95		49	35.5	24.5	11	14	9.8	
CO_2	35	43		44	44		47			
Chloride	552	510		592		616	585	585		
Intake, c.c.	4485	3400	5060	3800	3905					
Urinary output, c.c.	2400	2450	750	2600						
B.P.		130/85	130/80					120/78		115/90
Weight, pounds	130½	128				128½	128	126½		

On the third hospital day, the patient was noted to be slightly icteric, and one vascular spider was noted on the left chest. On this day, cephalin flocculation test was 4 plus in 24 hours, and total serum bilirubin was 2 mg. per cent. The bromsulfalein test (5 mg./kilo) on this date showed 47 per cent retention in 45 minutes. A lumbar puncture was negative on the fourth day. The patient was afebrile for the first four hospital days. On the fifth day, retrograde pyelograms were done, and the patient began to run a low-grade fever. The pyelograms were normal. Penicillin was given for the next week; fever gradually subsided during this period. On the sixth day a liver biopsy showed central necrosis and fatty degeneration. On the seventh day, the heart was slightly enlarged to percussion, and the pulmonic second sound was accentuated. The patient was digitalized on this day because it was felt that he was developing early congestive heart failure. A chest x-ray on the eighth day showed moderate cardiac enlargement and early pulmonary edema. There was no actual pitting edema at any time, but the patient's face was felt to be fuller.

On the ninth day, a pericardial friction rub was first noted; this was thought to be due to uremia, since the blood urea nitrogen was 135 mg. per 100 c.c. of blood at this time. Electrocardiogram on this day showed nonspecific T wave changes Hemoglobin on this day reached its nadir—11 gm. On the eleventh hospital day, there were pain and swelling in the left deltoid region, perhaps the result of penicillin. On this day, the urine output first rose above anuric levels, and increased steadily thereafter, as shown in table 1. Chest x-ray on this day showed a further increase in both the size of the heart and in the pulmonary edema. In spite of the rising urinary output, the patient was quite ill on the thirteenth day, being drowsy, but never stuporous, and hiccoughing frequently. Some benefit from the use of CO_2 inhalations was noted with regard to the latter symptom. After this day, the patient gradually recovered his appetite and normal mental status. On the sixteenth day, the urine became negative, and remained so. On the seventeenth day, the serum bilirubin had returned to normal. On the twenty-first day, the chest x-ray showed the heart to be still generally enlarged, but the lung fields to be somewhat clearer than before. On the twenty-fifth day, the electrocardiogram was consistent with pericarditis. On the twenty-seventh day, chest x-ray and fluoroscopy showed the heart to be still enlarged, with a large left ventricle. The lung fields were clear. On the twenty-eighth day, the patient developed a pain in his right chest and a fever of 102 degrees. Penicillin was then started and continued for five days. The patient was free of pain and fever on the thirty-first day. On that day, chest x-ray showed the heart to be moderately smaller than on the preceding film. On the thirty-sixth day, the pericardial friction rub had disappeared. Phenol red test on the forty-first day showed excretion of 8 per cent of the dye in 15 minutes and a total of 47 per cent in two hours. On the forty-third day, urinary concentration test showed a maximum concentration of 1.018. Hemoglobin had risen to 12.5 gm. on this day. On the forty-fifth day, venous pressure was 8 cm. of water, and decholin circulation time was 15 seconds. The patient was discharged on this day, his heart being still enlarged. Unfortunately, he went to another city, and no further information with regard to his course has been obtainable.*

Case 2. A 42-year-old white female stenographer was admitted to the Veterans' Administration Hospital, Dayton, Ohio, on June 3, 1947. The history essentially was that of low back pain of two years' duration with recent radiation into the left leg.

Physical examination on admission was normal except for findings suggestive of herniated intervertebral disc and radiculitis of the first sacral nerve.

Laboratory data on admission: Hemoglobin 12.5 gm.; red blood cells 4,150,000; white blood cells 8,550; 58 per cent polynuclears, 37 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophiles. Sedimentation rate of erythrocytes, 5 mm./hr. Bleeding time 1.5 minutes. Clotting time 3.5 minutes. Urinalysis negative.

Course: On the eighth hospital day, a myelogram revealed a filling defect at the fifth lumbar interspace. On the fourteenth hospital day, a partial hemilaminectomy was performed and the degenerated fibrocartilage was removed. There was considerable bleeding from the epidural space, and the blood pressure fell to 60/45; 500 c.c. of whole blood and 25 mg. of ephedrine sulfate were given and the blood pressure then rose to 200/100 and remained there. Two hours post-operatively, the blood pressure began to fall again, and considerable bleeding was noted from the operative site. The hemorrhage was controlled with some difficulty. At this time the patient received 2,500 c.c. of plasma and 500 c.c. of whole blood for shock.

For summary of the post-operative course, see table 2. On the first post-operative day, the blood pressure fell to 88/30, although there was no further evidence of hemorrhage. The patient was given 1,000 c.c. of whole blood and 2,000 c.c. of

*The patient was seen a year later. At this time the heart was at upper limit of normal size. The electrocardiogram showed only an inverted T wave in Lead AVL. He was asymptomatic.

TABLE II

Case 2, 42-Year-Old White Female

Hosp. Day	Operation	Post-Op. 1	2	3	4	5	6	7
NPN			54	108	87	85	114	91
BUN					50	54	68	88
CO_2								34.5
Chloride				512	537	511	628	668
Intake, c.c.	3500	3900	4150	330	550	1070	800	1000
Urine output, c.c.	0	125	100	18	2	35	10	50

Hosp. Day	8	9	10	11	12	13	14	15	16
NPN	105	106	110	115	134	110	108	120	120
BUN		88	86	87	100	80			78
CO_2	38	37	32.4	25	30	36	31.5	38	31.5
Chloride	715	745	726						
Intake, c.c.	1200	2310	2325	800	620	750	350	1550	1900
Urine output, c.c.	27	43	120	390	900	2090	2550	2460	2900

Hosp. Day	17	18	22	24	29	31	41	62
NPN		115	84	77	45	44	24	24
BUN			65	49	20	16	16	
CO_2								
Chloride				480				
Intake, c.c.	1600							
Urine output, c.c.	1650							

normal saline intravenously, with return of the blood pressure to normal levels. The total urinary output for this day was 125 c.c., and the patient was virtually anuric for the next nine days. Because of the anuria, a check was made, with regard to the type blood given the patient; it was later found that the original transfusion had been mislabeled as to type. On the second post-operative day, hemoglobin was 9 gm. per 100 c.c. of blood, and platelet count was 55,000 per cu. mm. The patient received a total of 3,000 c.c. of fluid parenterally on this day, including 1,000 c.c. of whole blood. That evening, she developed pulmonary edema and mild cyanosis. On the third post-operative day, the patient had frank pulmonary edema, which was treated with oxygen. Platelet count on this day had risen to 281,000, and thereafter remained at normal levels. The patient was improved clinically on the fourth post-operative day. On the fifth post-operative day, bilateral sympathetic block was performed in hope of improving kidney function, but anuria continued. On the next four days, the patient was fairly comfortable, free of edema, but intermittently delirious. On the tenth post-operative day, generalized edema appeared, and the patient became dyspneic; the blood pressure rose to 160/60. On the eleventh post-operative day, the patient was in severe congestive heart failure, which improved somewhat after digitalization with cedilanid. Diuresis seemed well under way on the twelfth post-operative day, with a total urinary output of 900 c.c., but improvement was delayed. On the thirteenth day, the patient exhibited anasarca, marked venous distention, frothy sputum, and appeared moribund. A phlebotomy with removal of 500 c.c. of blood was followed by considerable improvement. On the fourteenth post-operative day, she was able to be out of oxygen intermittently, and thereafter made a rapid recovery. All edema disappeared in the succeeding three days. The urinary specific gravity remained in the vicinity of 1.010, and in spite of the marked clinical improvement on the part of the patient, her azotemia remained essentially unimproved for several days.

A normal blood urea nitrogen was not reached until the thirty-sixth post-operative day, at which time the patient was up and about, and was asymptomatic.

On July 28, phenol red test showed 75 per cent excretion of the dye in two hours. On August 8, urea clearance was 70 per cent. On August 18, the Mosenthal test showed urinary specific gravities ranging from 1.008 to 1.016. The patient had developed a severe anemia, which was gradually improving as she was discharged asymptomatic on August 21, two months and 18 days after admission.

These two cases are not presented as examples of ideal management of the anuria of lower nephron nephrosis. Some attempt was made to restrict the total fluid intake to one liter per day plus the output, but, as can be seen from tables 1 and 2, this ideal was not achieved, partly because of division of authority among those caring for the patients. The excess of fluid intake, however, is not as great as would appear from the tables, since there was no accurate record kept of the fluid lost by vomiting. In neither of these cases was there any attempt to force diuresis by administration of excess fluids, yet pulmonary edema made its appearance in both patients, and almost caused death in the second patient. This fact indicates the need for even more careful restriction of fluids in the anuric patient than was observed in these patients.

The term "lower nephron nephrosis" was used by Lucké [20] to indicate a syndrome characterized by oliguria or anuria, heme pigment excretion, azotemia, hypertension, and uremia which may develop in conditions associated with the destruction of tissue or intravascular hemolysis. According to Lucké, this syndrome has been seen in crush injury and other types of injury to muscle, non-traumatic muscular ischemia, uteroplacental damage, eclampsia, burns, transfusion with incompatible blood, blackwater fever and other types of intravascular hemolysis, heat stroke, sulfonamide intoxication, alkalosis, mushroom poisoning, and other poisonings with vegetable and chemical agents. Death usually occurs in 10 days, according to Lucké. Other writers [19] have used the term "tubulo-vascular syndrome" as synonymous with lower nephron nephrosis. The prognosis when anuria develops in this syndrome is grim. Dobbs [10] stated that the mortality following extensive post-transfusion hemolysis is greater than 50 per cent. Leiter [19] stated that time is of the essence for recovery; the outlook in toxic nephrosis is either for death or complete recovery; chronic intermediate stages do not seem to occur. Diuresis usually occurs on the eleventh or twelfth day of the illness, according to Kugel.[18] Muirhead et al.[22] stated that diuresis usually occurred in from eight to 14 days in lower nephron nephrosis. Bradley [4] reported 17 cases of toxic nephrosis following hemolytic transfusion reaction, of whom six recovered with onset of diuresis as shown in table 3. In 13 cases of renal insufficiency following transfusion reported by Daniels et al.,[9] six cases recovered, with diuresis occurring as shown in table 3. Goldring and Graef [14] reported seven cases of nephrosis with uremia following transfusion with incompatible blood. Four of these cases recovered, with diuresis taking place as seen in table 3.

TABLE III

Cases of Lower Nephron Nephrosis That Recovered with Day of Onset of Diuresis from Time of Original Renal Injury

Author	Total Cases	No. Recovering	No. with Diuresis	Day Onset Diuresis in Each Case
Bradley	17	6	6	8, 9(2), 10, 12, prior to 14
Daniels	13	6	6	5, 7, 8(2), 10, 12
Goldring and Graef	7	4	4	7, 11, 13, 15
Present series	13	5	6	7, 10(3), 12(2)

A review was made of the cases of toxic nephrosis seen on the medical service of the Cincinnati General Hospital since October 1939. A total of 13 cases was found including the cases in this paper. Eight of these 13 cases died and five recovered. In the patients who recovered diuresis took place as indicated in table 3. In one fatal case of carbon tetrachloride poisoning, diuresis took place on the tenth day, but the blood urea nitrogen did not fall, and death from uremia occurred on the seventeenth day. In the fatal cases, death occurred on the second, fourth, sixth, eighth, tenth, fourteenth, and seventeenth days. Only those dying on the fourteenth and seventeenth days could be said definitely to have died of uremia, and both these cases had a normal urinary output at the time of death. Five of the eight fatal cases had either peripheral or pulmonary edema at the time of death, and one of the others had two episodes of pulmonary edema during his course. Edema appeared in three of the five cases who recovered, and nearly caused death in at least one of the three.

A consideration of the above data leads one to the conclusion that the primary aim in therapy of a patient with the anuria of lower nephron nephrosis is to keep the patient alive until diuresis occurs spontaneously. If the above cases can be taken as typical examples of the course of lower nephron nephrosis, keeping the anuric patient alive for two weeks would result in eventual recovery in almost every case, and keeping the patient alive 10 or 11 days would lead to recovery in most instances.

One approach to the problem of sustaining life in the anuric patient with lower nephron nephrosis has been the use of the artificial kidney.[3, 4, 5] Another has been the use of the peritoneum as a dialyzing membrane for the removal of urea and the toxic products of metabolism from the blood. Fine, Frank and Seligman [11, 13] state that "the uremia resulting from acute renal damage is frequently fatal because the renal lesion requires more time for healing than the lethal effects of the uremia will permit." Goodyear and Beard [15] refer to peritoneal lavage as a life-saving procedure. It is upon this concept that the use of peritoneal lavage or the artificial kidney in the uremia of lower nephron nephrosis is based; facts opposing this concept are presented later in this paper. The futility of using either of these two devices in cases of irreversible renal disease is admitted by even their most enthusiastic exponents.

Fine, Frank and Seligman [11, 12] treated four cases of uremia with peritoneal lavage. In one of their four cases, the uremia was not due to toxic nephrosis, and death occurred, since the renal lesion was of irreversible nature. Two of their three cases of lower nephron nephrosis recovered. Diuresis in the two cases recovering took place on the ninth and fourteenth days. It is of interest to note that three of their four cases developed pulmonary edema while being treated. The case of lower nephron nephrosis that died did so on the eighth day, not of uremia apparently but quite possibly of abnormal fluid balance. Reid et al.[27] reported a case of anuria following transfusion with incompatible blood. Renal decapsulation was done on the ninth day of anuria. Diuresis was noted on the tenth day of anuria. Peritoneal irrigation was done on the ninth, tenth and eleventh days. Only 6.4 gm. of urea were removed by this technic and it was apparent that the diuresis and not the lavage was responsible for recovery. As for renal decapsulation, Culpepper and Findley [6] reviewed the literature on that procedure in 1947, and concluded that the recovery rate in lower nephron nephrosis had not been improved by renal decapsulation, with the doubtful exception of transfusion kidney. Goodyear and Beard [15] report a case of transfusion reaction with anuria treated for four days by peritoneal lavage with recovery. Diuresis occurred on the seventh day and the lavage was discontinued. Here the patient was described as stuporous with uremia on the third day of anuria, although the non-protein nitrogen on this day was only 86 mg. per 100 c.c. of blood. It would seem that some factor other than uremia was responsible for the patient's stupor and desperate condition. Odell and Ferris [25] mentioned that of 15 cases of reversible uremia treated by peritoneal lavage at the time of their paper, eight recovered. They report a case of anuria following carbon tetrachloride poisoning which was treated by peritoneal lavage; the patient died on the seventh day of irrigation and the sixteenth day of anuria; at necropsy, edema of the lungs and brain and peritonitis were found.

Robertson and Rutherford [28] report a case of anuria following transfusion reaction that died of pulmonary edema on the eighth day of anuria. The pulmonary edema could apparently be attributed to the fluid used in peritoneal irrigation. Muirhead et al.[23, 24] reported three cases of transfusion reaction anuria treated by peritoneal lavage. One case died of widespread tuberculosis, and a second died accidentally. The case that recovered apparently did so despite peritoneal lavage, which was begun only after he was well on his way to spontaneous recovery. Muirhead et al.[23] felt that acidosis due to washing out of base and the production of edema by the absorption of water and sodium from the lavage fluid were major complications of peritoneal lavage therapy. Grossman et al.[16] reported a case of anuria and jaundice in a pregnant woman, who was irrigated via the peritoneal route on the ninth to twelfth days of her anuria. By the twelfth day from the onset of anuria diuresis had begun, and the renal output of urine had reached the

level of 1,080 c.c. in 24 hours. Lavage was then discontinued. The authors felt that it was impossible to say that the patient would not have recovered without peritoneal irrigation, but it was their opinion that the procedure was responsible for her improvement and recovery. Strean et al.[21] reported a case of anuria in a 25-year-old white woman following a transfusion reaction. Her irrigation was started on the sixth day of anuria and was continued 10 more days. The patient was voiding spontaneously over a liter of urine per day on the eighth day following the transfusion, and it is difficult to see that the procedure contributed materially to her recovery. Bassett et al.[2] employed peritoneal lavage in a case of subacute glomerulonephritis. The flow of urine was not reëstablished and the patient died on the twenty-first day of anuria. This patient lost 117 grams of protein in the lavage fluid; this fact is not usually mentioned. Buckley and Scholten[5] report a very interesting case of anuria following the ingestion of bichloride of mercury. The patient received peritoneal lavage for 12 days, beginning on the fourth day of his anuria. Diuresis began on the ninth day, but the urine contained little urea, and the blood non-protein nitrogen did not fall, reaching a level of 365 mg. per 100 c.c. of blood on the twenty-fifth day. Death occurred on the twenty-seventh day. A peritonitis due to *E. coli* was found post mortem.

The above cases include all instances of the use of peritoneal lavage that could be discovered since the reports of Fine, Frank and Seligman.[11] Of these, it would seem that only three, the two cases of Fine, Frank and Seligman, and the case of Grossman,[16] could conceivably be said to have benefited from the procedure. The hazards of this method are numerous, and include peritonitis, loss of protein, acidosis from the loss of base, and development of pulmonary edema from the absorption of water and base from the lavage fluid. Admittedly, the last named difficulty can possibly be effectively countered by the use of the peritoneal lavage solution described by Abbott and Shea.[1]

The above statements would seem to imply that peritoneal lavage is a risky procedure of doubtful benefit in the anuria of lower nephron nephrosis. The two cases reported here, plus numerous others cited in the discussion, show that it is possible for man to survive anuria for the critical period of 10 to 14 days necessary for the recovery of renal function following an acute injury; they further show that such survival is possible without the use of artificial methods for the removal of urea and toxic metabolic products from the blood. We should now like to examine the causes of death in acute toxic nephrosis, and see what can be done to improve the survival rate.

Kugel[18] attempted to analyze the causes of death in 13 cases of acute toxic nephrosis. He felt that one portion of the cases dies early of the acute effects of the poison, rather than of isolated renal insufficiency. A second group he found to die early in their course—from the fourth to the tenth days of their anuria—too soon, he felt, to be the result of uremia. Nine of

13 such patients showed edema or other cardiovascular complications. It was apparent that the conventional forcing of fluids for anuria was at least in part responsible for their deaths. In the 13 cases of transfusion reaction anuria reported by Daniels [9] seven cases died. Six of these seven cases died before the tenth day of anuria, too early to die of uremia. Five of the seven had evidence of edema in the lungs. Of the 14 illustrative cases of lower nephron nephrosis cited by Lucké [20] six had peripheral or pulmonary edema. All of these cases were fatal.

Mallory [22] commented on the common finding of peripheral or pulmonary edema in his cases of lower nephron nephrosis following battle injury, and noted that the patient survived long enough to develop uremia only if these complications were avoided. Five of the eight fatal cases of lower nephron nephrosis which were found at the Cincinnati General Hospital had either peripheral or pulmonary edema at the time of death.

Kugel [18] stressed the fact that the conventional forcing of fluid and alkali in an effort to force urine from the anuric kidney should be avoided, although in the past many reliable authorities [26, 29, 32] have recommended this procedure. Maegraith and Havard [21] felt that alkali should not be pushed if the urine were still acid after 24 hours of alkali therapy, because the urine may remain acid even in the presence of alkalosis if the renal damage is severe, and because alkalosis may still further injure the kidney. They did not mention the danger of retention of the added sodium and water, thereby increasing the burden on an already strained circulation. Corcoran and Page [7] state that once there is damage to the kidney, the evolution of the renal injury is largely unaffected by treatment, and that many cases of lower nephron nephrosis recede spontaneously in one week. They also say "were it possible to maintain life during the period of renal injury until sufficient regeneration had occurred, it is possible that recovery would then be assured."

In order to illustrate the potentially disastrous effects of the conventional forcing of fluid and alkali in the face of oliguria, the following case will be described briefly.

An 18-year-old white male was admitted to the Surgical Service of the Cincinnati General Hospital on March 12, 1947, with a diagnosis of crush syndrome. In an apparent effort to prevent anuria, the patient received massive quantities of fluid and alkali during the six days following admission. During these six days, he received a total of 26,400 c.c. of fluid, with a urinary output of 5,165 c.c. during the same period. Also during this period he received 57.5 gm. of sodium bicarbonate, 600 c.c. of sodium lactate and an additional ampoule of racemic sodium lactate. At the end of this six day period, the patient had cardiac enlargement with early pulmonary edema; his venous pressure had risen to 17 cm. of water; his blood pressure had risen from 128/74 on admission to 178/110; his blood urea nitrogen had risen from 35 on admission to over 100 mg. per 100 c.c. of blood; finally, his CO_2 combining power had risen to 93 vol. per cent. All this had occurred despite the fact that the urinary output never fell below 350 c.c. per day. Fortunately, at the end of the sixth day, fluids were restricted, a diuresis followed, and eventual recovery ensued. It seems fair to say that the alkalosis and pulmonary edema could have been avoided by the judicious restriction of fluid and sodium in the beginning.

Therefore, it would seem that careful attention to the management of water and sodium intake is of the essence in the care of the anuric patient. The general rule for the administration of water in the anuric patient is that fluids should be restricted to an amount below that which will produce edema. Butler and Talbot [6] have studied the normal water requirement of the adult. The 24 hour water lost by an anuric adult of 60 kg. would approximate 100 c.c. in the stool and 600 to 1,000 c.c. in the expired air and in the insensible perspiration. More of course is lost if there is visible sweating, vomiting, diarrhea, etc. The water ingested in the food, or produced by the breakdown of the patient's own tissue if no food is given, approximates the amount lost in breathing and in insensible perspiration. Thus, only a few hundred c.c. of water per 24 hours are needed in anuria, primarily to replace that lost in the stool and in visible perspiration. If there is any urine passed, or if any vomiting occurs, additional allowance must be made for that. Ideally, if the patient is unable to take food by mouth, he should receive 6 gm. of dextrose and 0.6 gm. of amino acids per kg. body weight per 24 hours to maintain caloric requirement and nitrogen balance [6] but this amount is not capable of being given in the amount of fluid recommended. Kugel [18] states that strict caloric balance is not important because of the limited duration of the disease. However, in order to spare tissue protein and thus limit the accumulation of the toxic products of protein metabolism, as much as possible of the recommended caloric intake should be given. Since sweat contains 0.2 per cent to 0.5 per cent sodium chloride [8] and the insensible perspiration volume averages 500 c.c. per 24 hours, it is felt that 2.5 gm. of sodium chloride per 24 hours should be ample, unless there is visible sweating, vomiting, or diarrhea. Thiamine 2 to 5 mg., riboflavin 5 mg., niacinamide 20 mg., and ascorbic acid 100 mg. should be added to each day's infusion. Kugel [18] recommends that no attempt be made to correct hypochloremia or low CO_2 combining power, since such an attempt will necessitate the use of sodium with its attendant risk of pulmonary edema. The occurrence of edema evidenced either by pitting or marked increase in weight, or increase in liver size, venous distention in the neck, increase in the pulmonic second sound, or of moist râles in the lung bases must be carefully watched for, and fluids restricted still further if these occur. Digitalization and venesection should be used if congestive heart failure occurs.

Summary

1. Two cases of lower nephron nephrosis surviving under conservative management despite anuria of 10 days and 11 days are reported.

2. The renal lesion of lower nephron nephrosis is reversible, and spontaneous diuresis takes place in most cases that survive within 10 or 11 days after the renal injury, and in practically all cases within 14 days.

3. If the patient with lower nephron nephrosis can be kept alive for 10 to 14 days, it is to be hoped that all cases not dying of the acute effects of

the injury or poison will recover. However, in a few cases, uremia fails to be relieved even after diuresis has occurred.

4. Peritoneal lavage is a risky procedure of doubtful benefit, and is not essential to the survival of the anuric patient for 10 to 14 days, i.e., the period compatible with recovery.

5. Congestive heart failure with pulmonary edema as a result of forcing fluids and sodium in an attempt to provoke diuresis are common causes of death in anuric patients.

6. At present conservative medical management seems to offer the best chance of survival for the anuric patient suffering from lower nephron nephrosis.

7. The anuric patient should be fed by mouth if possible. He should receive only a few hundred c.c. of fluid daily; if he must be fed parenterally, the fluid should contain as much dextrose as possible up to 6 gm. per kg. per 24 hours, 2.5 gm. of sodium chloride, 2 mg. of thiamine, 5 mg. of riboflavin, 20 mg. of niacinamide, and 100 mg. of ascorbic acid. The total water and sodium chloride intake should be increased if there is vomiting, diarrhea or visible sweating.

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INTRACARDIAC CATHETERIZATION *

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INTRODUCTION

IT is the purpose of this paper to present a group of 25 patients who have had venous catheterization of the right heart. We feel that this procedure has now reached a stage where it can be used as a valuable diagnostic aid in the complete clinical evaluation of patients with actual or suspected congenital heart disease. Venous catheterization of the right heart can be used in capable hands in any well regulated cardiac clinic and should be used to supplement our present armamentarium.

LITERATURE REVIEW

In 1929 Forssman,[1] after having his median basilic vein exposed by a surgeon, performed upon himself the first cardiac catheterization by introducing a ureteral catheter into the vein. Since then this method has been used for various research purposes. In 1930, Klein [2] determined the heart's minute volume output in man, after Fick's [3] principle, with venous blood obtained by catheterization of the right auricle. Similar determinations were carried out later in normal subjects by other investigators.[4] In this country Cournand and Ranges,[5-26] Burwell and his group,[6] and Stead and Warren [7] and their group have led the investigations. Warren et al.[8] used this technic in observing the effect of venesection and pooling of the blood in extremities on the atrial pressure and cardiac output in normal subjects and in acute circulatory collapse. Brannon et al.[9, 10] measured cardiac output this way in patients with chronic anemia. He also studied hemodynamics of acute hemorrhage. Merrill et al.[11, 12] studied the circulation in penetrating wounds of the chest and in a patient with pericardial tamponade from a stab wound of the heart. Chavez [13] and his collaborators modified Robb and Steinberg's [14] method of angiocardiography by inserting the catheter into the external jugular vein and introducing the dye directly into the cardiac chambers. Venous catheterization has been utilized by Munnell and Taylor [15] to study the blood flow in the liver of normal pregnant and nonpregnant patients by introducing the catheter through the inferior vena cava and into the right hepatic vein. This method with resultant sampling of blood leaving the liver offers further opportunities for study of liver function.

By utilizing the Hamilton [16] manometer or other similar pressure apparatus, intracardiac venous pressures can be obtained. By utilization of

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this method the cardiorespiratory system can be studied much more thoroughly. Motley [17] and his workers found that pulmonary hypertension was rapidly induced in subjects with normal blood pressures by the inhalation of 10 per cent oxygen for short periods of time with only a slight rise in systemic blood pressure. The pulmonary pressures rapidly returned to normal when the low oxygen breathing was discontinued. They found that pulmonary pressure was almost doubled during anoxia while the systemic peripheral resistance increased but slightly. Other investigators have introduced the catheter into the venous system by way of the internal saphenous vein and from here renal vein and portal system studies have been attained. Richards [18] employing this method of study has recently done some excellent work in congestive heart failure. In cases of well marked right sided congestion mean pressures in the right auricle and peripheral veins have been found to be essentially identical. Left sided congestive heart failure produced greatly elevated pressures in the lesser circuit and in the right ventricle. In cor pulmonale, or right sided cardiac hypertrophy associated with chronic pulmonary disease, pulmonary arterial hypertension is an important factor but it is interesting in that it is usually less than that seen in failure of the left ventricle.[29]

In 1939 Gross and Hubbard [19] described the successful closure of a patent ductus arteriosus; in 1945 Crafoord and Nylin,[20] and Gross and Hufnagel [21] described the removal of the obstruction in adult forms of coarctation; and in 1945 Blalock and Taussig [22] introduced surgery for the relief of cyanosis associated with pulmonic stenosis. Because of these surgical procedures, cardiac catheterization is essential to help in establishing a definite diagnosis and explaining the disturbed cardiovascular physiology.

Method and Interpretation

A 100 cm. radio-opaque ureteral catheter (6 or 9F.) is inserted in the median basilic vein under local anesthesia with strict sterile precautions. An isotonic saline solution containing heparin is maintained at a slow drip controlled by a tunnel clamp. With the patient in the supine position, under fluoroscopic control, the catheter is then passed through the subclavian vein, superior vena cava, the right atrium, the right ventricle, pulmonary conus, pulmonary artery, and its branches, whenever possible. Before blood samples are drawn for analysis, several cubic centimeters of blood are withdrawn through the catheter and discarded. Samples of blood are then drawn under oil from the various sites. The blood samples are analyzed by the manometric method of Van Slyke [23] for oxygen content, and these results are correlated with clinical findings. Only duplicate analyses which check within 0.1 volume per cent are accepted as satisfactory. The normal variation of the oxygen content in the various chambers of the heart has been established. The normal variation between the superior vena cava and right auricle is 1.9 volumes per cent, between the right auricle and right ventricle

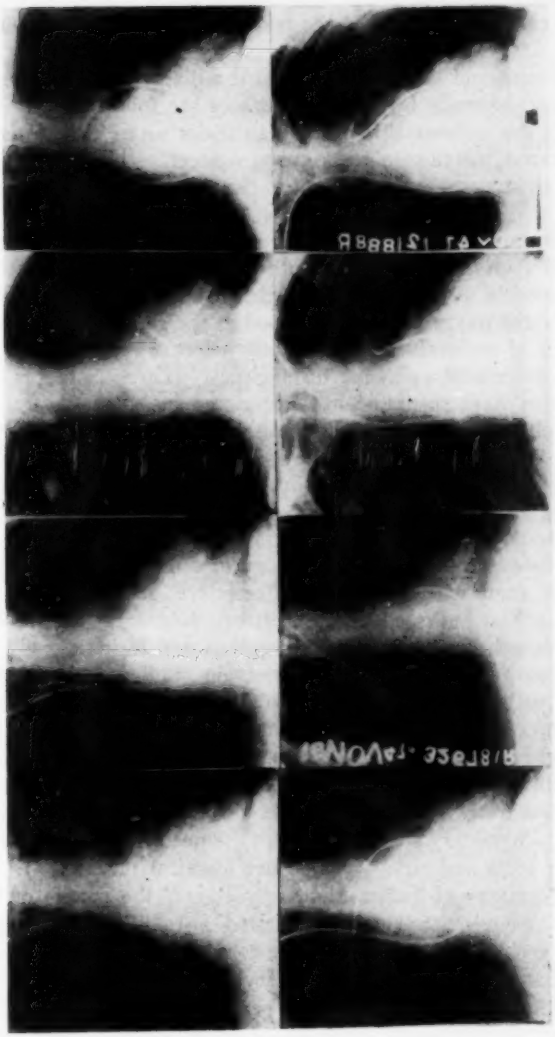

FIG. 1. Shows a few positions of the catheter from where samples of blood are drawn. Reading across they are as follows: upper part of right auricle, middle of right ventricle, pulmonary conus, bifurcation of pulmonary arteries, right pulmonary artery, first part of left pulmonary artery, farther into left pulmonary artery, and into the terminal branches of left pulmonary artery.

0.9 volume per cent, between the right ventricle and pulmonary artery 0.5 volume per cent, and within the pulmonary branches themselves 0.5 volume per cent.

The diagnosis of a patent ductus arteriosus is made when a significantly greater oxygen content is present in the pulmonary artery than in the right ventricle.

Brannon, Weens, and Warren [24] found that a diagnosis of interauricular septal defect could be made by either or both of the following procedures: (*a*) introducing the catheter through the auricular septal defect, and (*b*) finding a significant increase in the oxygen content of blood in the right auricle (left to right shunt) as compared to that obtained from the superior vena cava.

The recognition of interventricular septal defect by venous catheterization may depend upon finding a significant increase in the amount of oxygen in the right ventricle as compared with that from the right auricle. A significantly elevated oxygen content of blood in the right ventricle may reflect the presence of an interventricular septal defect or theoretically, patent ductus with an associated pulmonic insufficiency. Three instances of this latter phenomenon were suspected by Dexter and his group.[25] In one of their patients following surgery which eradicated all murmurs, a subsequent venous catheterization failed to reveal any significant variation of oxygen in the right auricle, right ventricle, or pulmonary artery. They believed, therefore, that a diagnosis of interventricular septal defect in the presence of a patent ductus should be made with caution.

It is not to be expected that the Tetralogy of Fallot could be recognized in its entirety by study with the venous catheter. Right ventricular hypertrophy is perhaps best indicated by the electrocardiogram. Dextroposition of the aorta is largely a morphological diagnosis and is functionally indistinguishable from a ventricular septal defect in studies with the venous catheter. The catheter may pass from the right ventricle through the stenotic pulmonary valve into the pulmonary artery. In this case, pulmonary stenosis may be recognized by the presence of a higher systolic pressure in the right ventricle than in the pulmonary artery. In other cases, the catheter may pass from the right ventricle, through the septal defect, and into the aorta. Pulmonary stenosis has been assumed to exist if the systolic pressures in the aorta and right ventricle are identical (Dexter [25]). In 48 patients with Tetralogy of Fallot studied by Bing,[27] the results of certain respiratory and exercise tests [28] demonstrated a reduction in pulmonary artery flow of from 1000 to 2000 c.c. below normal cardiac index, depending on the degree of stenosis. In one patient in whom the calculated rate of flow through the pulmonary artery was only 20 per cent of normal, atresia of that vessel was found at operation. In most cases the systemic flow exceeded that through the pulmonary artery, indicating that the over-all direction of the intracardiac shunt is from right to left. Consequently the systemic blood

flow will be particularly high in individuals with severe pulmonic stenosis, large interventricular septal defects, and marked over-riding of the aorta.

Complications

We have had no major complications. Occasionally ventricular extrasystoles appear but do not persist. Auricular fibrillation has been reported [8] but this was controlled and disappeared when the catheter was removed. Two of our cases developed superficial phlebitis which was easily taken care of with local procedures. Our patients are given 50,000 units of penicillin every three hours, 12 hours before and after the procedure.

Results

To date 25 patients have had this procedure performed and the following is a breakdown of these cases:

Group I. Interatrial septal defects 5
Group II. Interventricular septal defects 4
Group III. Patent ductus arteriosus 8
(*a*) Four confirmed and ligated at operation.
(*b*) Four confirmed by catheterization, not operated upon.
Group IV. Congenital heart disease suspected 3
(*a*) Normal gas volumes obtained.
Group V. Congenital heart disease with normal oxygen volumes obtained 2
Group VI. Combined lesions:
(*a*) Patent ductus arteriosus and interventricular septal defect 2,
The ductus confirmed by operation.
(*b*) Patent interatrial septal defect and anomalous pulmonary vein 1

A few illustrative cases are presented.

Group 1. Interatrial Septal Defects.

Case 1. A 20 year old white male was admitted as a transfer from Japan with a history of fever and joint pains on July 21, 1947. These symptoms subsided in four days but on July 31 he was admitted to a hospital with fever, knee and elbow joint pains. The knees were swollen but not red. The sedimentation rate was elevated from August 1 to September 30. He did not feel well until September 1 and his joints were painful on motion until September 15. The electrocardiograms showed right axis deviation. Cardiac fluoroscopy showed a normal sized heart, but with increased pulsations of the pulmonary artery. During this admission a grade II systolic murmur was described in the second and third left interspaces transmitted to other cardiac areas. On admission to this hospital the patient had no further complaints. Further history revealed that the patient had been short of breath on climbing two flights of stairs since the age of 16. Since that age he had considered himself more easily made dyspneic than other individuals. He had not been examined thoroughly up to the time of his initial hospital admission. He had "pneumonia" four times from ages two to six years. Physical examination showed a pale, thin white male. The blood pressure was 138/80 mm. Hg. The heart was not enlarged to percussion. A grade III high pitched systolic murmur was loudest in the second left interspace, transmitted to the aortic area and down the left sternal border to the apex. It was not changed by position and was heard under the left scapula on deep expiration. No thrills were present. The second pulmonic sound was accentuated.

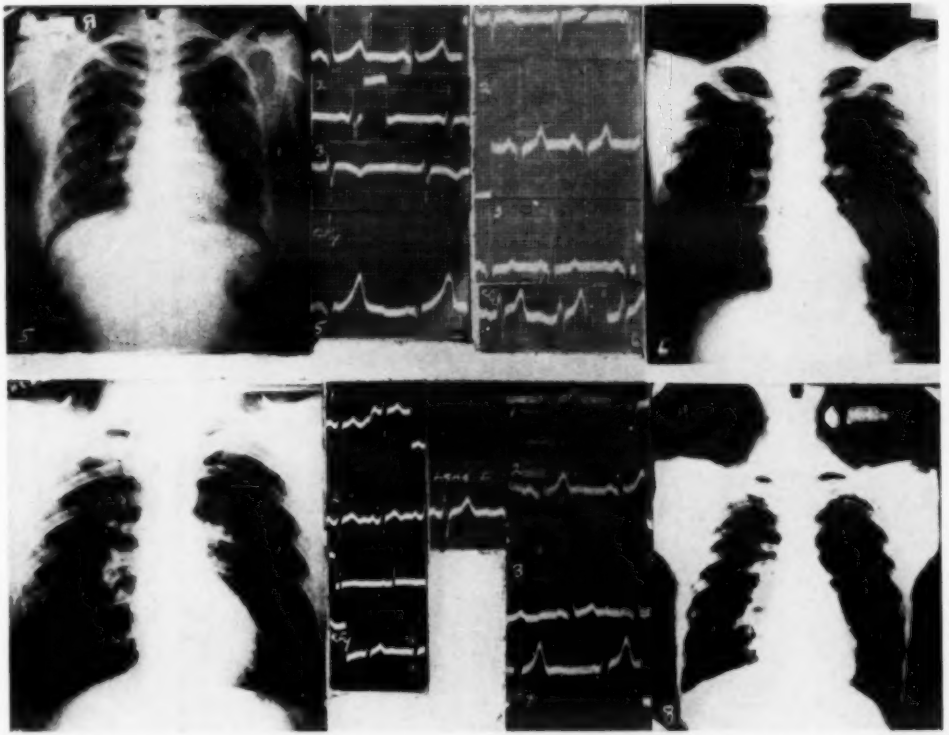

FIG. 2. Roentgenograms and electrocardiograms of several cases described in text. Upper left is Case 4, upper right is Case 7, lower left is Case 2, lower right is Case 1.

Laboratory data were normal and an electrocardiogram showed right axis deviation (figure 2). A chest x-ray showed a small amount of pleural thickening present at the right costal pulmonary angle. A diagnosis of rheumatic heart disease was made with possible congenital heart disease also present. Cardiac catheterization showed the oxygen content of the superior vena cava to be 16.0 volumes per cent and the right auricle 19.5 volumes per cent.

The significant difference between the superior vena cava and right auricle is consistent with a left to right shunt in the auricles. In dogs, Brannon, Weens and Warren [24] have found the O_2 content of auricular blood significantly higher than that of the venae cavae in auricular septal defects. The patient was discharged with a diagnosis of uncomplicated interauricular septal defect.

Case 2. A 19 year old white male was admitted to Brooke General Hospital September 29, 1947, with the diagnosis of rheumatic fever. On July 4, 1947, he entered a hospital overseas because of general malaise and stiffness in his neck. This lasted for a period of three days. The patient had a headache and a slight chill and fever of 102° F. on the morning of admission. At that time a loud systolic murmur was heard at the pulmonic area transmitted over the rest of the precordium. Laboratory studies revealed a white blood count of 11,600, negative blood cultures, and a sedimentation rate of 3 mm. per hour. On admission to Brooke General Hospital the patient stated that he had never had sore throats, chorea, or evidence of skin nodules. His only previous history was pain and slight swelling of the left ankle for one week while overseas. Physical examination showed a pale, well developed, young adult white male. The pulse rate was 100 per minute and regular. The blood pressure was 140/80 mm. Hg, with no change after exercise. The heart was not enlarged to percussion. The rhythm was regular, and the sounds were of good quality. The second pulmonic sound was accentuated. There was a grade II blowing systolic murmur heard best in the third and fourth interspace at the left sternal border. This was transmitted to the mitral area where it was of grade I intensity. No thrills were palpable. The electrocardiogram showed a moderate degree of right axis shift (figure 2). Fluoroscopy showed some widening of the aortic shadow and increased pulsation of the pulmonary artery circulation time using decholin was 12 seconds, arm to tongue. A cardiac catheterization was done to the left arm on November 26, 1947. The oxygen content of the superior vena cava was 15.62 volumes per cent, the right auricle 17.10 volumes per cent and the right ventricle 16.22 volumes per cent. The patient was discharged with a diagnosis of uncomplicated interauricular septal defect.

In both of these two cases the heart was not enlarged. They were characterized by a loud systolic murmur to the left of the sternum usually located from the second to the fourth interspaces. In both patients the second pulmonic sound was accentuated. The usual characteristic signs of an interauricular septal defect such as marked dilatation and increased pulsation of the pulmonary artery, shortening of the aortic knob and marked enlargement of the right heart chambers were absent. It is for this reason that cardiac catheterization is necessary in these cases.

Group 2. Interventricular Septal Defect.

Case 3. A 29 year old white veteran was transferred to the hospital for evaluation. The patient had been in and out of hospitals for the past three years and had

many different diagnoses made including rheumatic heart disease and congenital heart disease. At the time of admission he was receiving compensation for rheumatic heart disease. His past history was entirely negative and the cardiac murmur was discovered in a routine physical examination. The patient had no complaints and was engaging in vigorous activities.

Physical examination showed a stocky male in no distress. The blood pressure was 128/76 mm. Hg in both arms. Positive findings were limited to the heart. On percussion the heart was enlarged slightly to the left. No thrill was palpated, but the chest wall was quite thick and muscular. There was a grade three long blowing systolic murmur heard best in the third and fourth left interspaces transmitted to the apex. This murmur did not change with respiration or position.

Fluoroscopy revealed a heart in the horizontal position, but with some enlargement of the left ventricle. The electrocardiogram was normal. The patient was catheterized, and the following results obtained. The oxygen content of the blood in

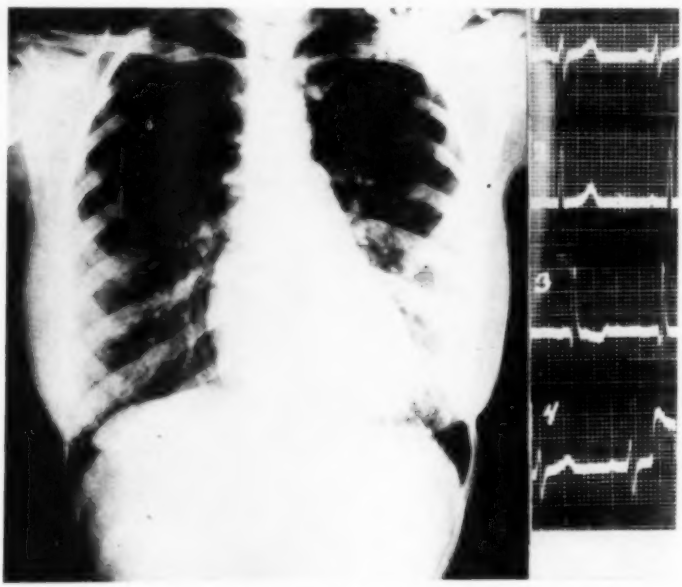

FIG. 3. Chest roentgenogram and electrocardiogram in Case 5.

the superior vena cava was 16.1 volumes per cent, in the right auricle 16.4 volumes per cent, and in the right ventricle 18.5 volumes per cent. He was discharged with the diagnosis of uncomplicated interventricular septal defect.

Case 4. A 19 year old female of Latin-American descent was admitted to the Surgical Service on November 27, 1947, because of acute appendicitis. Appendectomy was performed, and post-operative convalescence was uneventful. Physical examination on admission revealed a systolic thrill and a loud systolic murmur heard maximally in the third and fourth left interspace with transmission over the entire precordium. She was seen by the cardiology department and transferred to the Medical Service. She gave a past history that she was a blue baby at birth. However,

her development had been normal. When she was six years old the murmur was first noted and brought to her parents' attention. Since then, throughout her school years, exercise had been somewhat restricted. There was no history of joint pains, chorea, chest pain, edema, dyspnea or palpitation. She went through two pregnancies without difficulty and delivered two full-term babies spontaneously. Physical examination showed a blood pressure of 120/70 mm. Hg. The heart was not enlarged to percussion. A grade III systolic thrill was palpable inside the apex and over the midsternum. A grade IV loud blowing systolic murmur was heard maximally over the third and fourth left interspace with transmission over the entire precordium, but not transmitted into the axillary or neck vessels. The laboratory data were normal. The electrocardiogram showed left axis deviation (figure 2). A fluoroscopy showed prominence of the pulmonary conus, and a slight enlargement of the left ventricle. The patient was subsequently catheterized and the following results obtained. The oxygen content of the blood in the superior vena cava was 10.0 volumes per cent, in right auricle 10.5 volumes per cent and in right ventricle 12.2 volumes per cent. It was concluded that the patient had an interventricular septal defect.

Group 3. Patent Ductus Arteriosus.

Case 5. A 22 year old white female who had had no serious illnesses in the past. As a child she fatigued easily and became short of breath more rapidly than other children. When she was 15 years old, her physician told her that she should not participate in severe forms of exercise because of a "heart murmur." She was four months pregnant when first seen. Physical examination showed a well developed and well nourished female. The blood pressure was 120/50 mm. Hg, pulse 74, respirations 20. The heart was slightly enlarged to percussion to the left with no thrills. A grade III long harsh systolic murmur was heard in the second left interspace with a shorter diastolic phase. The systolic murmur could be heard down the left border of the sternum to the fourth interspace where it was more high pitched. She was followed through a normal gestation and subsequently catheterized, the results of which are as follows.

	O_2 vol. %	O_2 % saturation
S.V.C.	11.70	73%
R.A.	12.1	76%
R.V.	12.9	80%
Pulmonary artery bifurcation	13.08	81%
Right pulmonary artery	13.6	84%

There is a significant increase in the oxygen content from the right ventricle to the pulmonary artery. As has been mentioned before, a significantly elevated oxygen content of blood in the right ventricle may reflect the presence of an interventricular septal defect or, theoretically, of a patent ductus with an associated pulmonic insufficiency. The diagnosis of a patent ductus arteriosus with a possible interventricular septal defect was made on this patient.

Case 6. A 4 year old white male. The patient was a full-term breech presentation. No cyanosis was noted at birth. He developed slowly and did not walk until age of 22 months. His mother remarked that he would always take it slow "like an old man." Physical examination showed a small under-developed child weighing 35 pounds. There was no clubbing or cyanosis. The left side of the chest was prominent. Over the base a systolic thrill could be palpated with a grade IV harsh systolic murmur in the second and third interspaces, transmitted to left. At the fourth left interspace there was a questionable diastolic component. However, the stethocardiogram showed the diastolic murmur well. The second pulmonic sound was accentuated. The electrocardiogram was normal (figure 4). Fluoroscopy

showed an enlarged cardiac shadow with a hilar dance present. The diagnosis had always been an interauricular septal defect. However, catheterization studies revealed oxygen content of blood in the superior vena cava 10.8 volumes per cent, right auricle

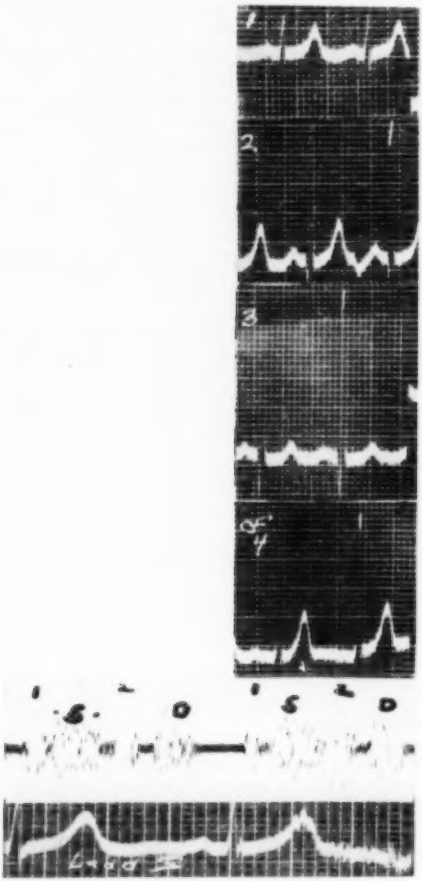

FIG. 4. The electrocardiogram and stethocardiogram in Case 6. The systolic and diastolic murmur are illustrated well.

10.4 volumes per cent, right ventricle 10.3 volumes per cent, right pulmonary artery 12.6 volumes per cent, and at the bifurcation of the pulmonary arteries 13.6 volumes per cent.

The patient subsequently had a large patent ductus ligated. Because the diastolic component of his murmur was not easily elicited the exact diag-

nosis had not been suspected. This illustrates the value of stethocardiograms in some instances. The case again demonstrates the value of cardiac catheterization. The child was seen in follow-up for a period of several months. All murmurs had disappeared and for the first time he was gaining weight. His activity had increased 100 per cent.

Group 4. Congenital Heart Disease Suspected but Normal Gas Volumes Obtained.

Case 7. A 19 year old white male. In June 1947 the patient had a routine physical examination and a heart murmur was found. A diagnosis of rheumatic heart disease with mitral insufficiency was made. His past history was non-contributory. Physical examination showed a well-nourished and developed white male. The blood pressure was 120/72 mm. Hg. The heart was not enlarged to percussion and no thrills were palpable. A grade II rough systolic murmur was heard best in the fourth left interspace at the sternal border. This murmur was fairly well localized and was not changed by body position. The remainder of the physical examination was negative. All laboratory work was within normal limits. The electrocardiogram showed a deep prominent S_1 and S_2 (figure 2). Fluoroscopic examination revealed a prominent pulmonary conus. Because a diagnosis of congenital heart disease was entertained by many, the patient was catheterized. These showed equal values of the oxygen content throughout and demonstrated that no abnormal shunt was present.

Group 5. Congenital Heart Disease with Normal Gas Volumes Obtained.

Case 8. A 7 year old white male. The patient had been noted to have a murmur since birth but no cyanosis was ever observed. He never had any serious illnesses and was quite active, being normally developed. He at no time had any complaints. Physical examination showed a well developed boy. The blood pressure was 90/40 mm. Hg, pulse 80. The heart was not enlarged to percussion. A thrill was palpable during systole over the fourth left interspace to the left of the sternum. In this area a grade III harsh systolic murmur was heard which persisted throughout systole. The murmur was transmitted over the precordium. No diastolic component was noted. The electrocardiogram was normal. A diagnosis of an interventricular septal defect was made. The following results were obtained by catheterization.

	1st sample O_2 content vol. %	2nd sample O_2 content vol. %
S.V.C.	13.25	13.25
R.A.	14	14.1
R.V.	14.5	14.6
Pulmonary conus	14.3	14.4
Right pulmonary artery	14.4	14.5

The conclusion drawn from this was that the interventricular septal defect was quite small and uncomplicated, giving a loud murmur and thrill but not important in causing a significant left to right shunt. It is sometimes important in these cases to determine the extent of the A–V shunt and then a better perspective of the patient's prognosis can be obtained.

Group 6. (a) Combined Patent Ductus Arteriosus and Interventricular Septal Defects Proved by Operation.

There were two cases in this group. The first patient, Case 9, a 4 year old female, showed the findings of a patent ductus on catheterization. A loud systolic murmur with a palpable thrill was present over the third and fourth left interspaces. No diastolic murmur was ever heard or recorded. A patent ductus arteriosus was ligated but the loud systolic murmur and thrill persisted. Clinically the patient improved remarkably so that it was

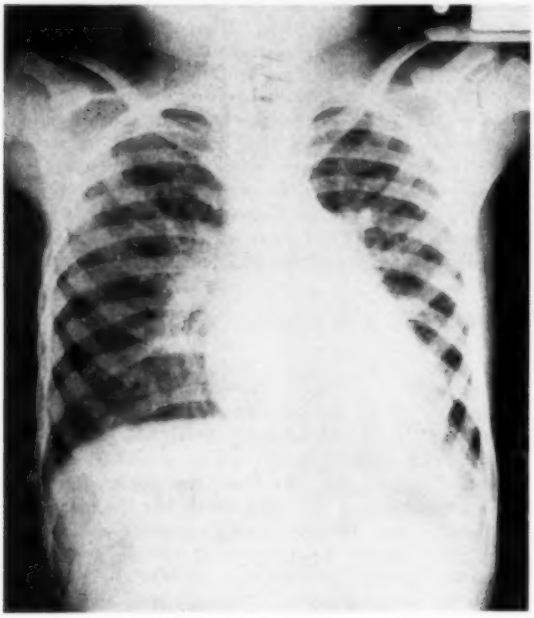

FIG. 5. Roentgenogram in Case 10.

felt that two lesions existed with the patent ductus having caused the greatest disturbance in physiology.

The second patient, Case 10, is described in more detail:

This 7 year old male was brought to this clinic on January 7, 1948. The child was under-developed for his age, a sister one year younger being much taller. All of his life he had been subject to frequent upper respiratory infections and had never had strength to play for long periods of time with other children. As far as is known the patient's mother had no illness during her pregnancy. When born he was not a blue baby. At three months he had pneumonia and following this was slow to develop. His mother noticed that his heart "beat hard" and at one year of age a doctor said that the patient had a "congenital heart." Physical examination revealed a

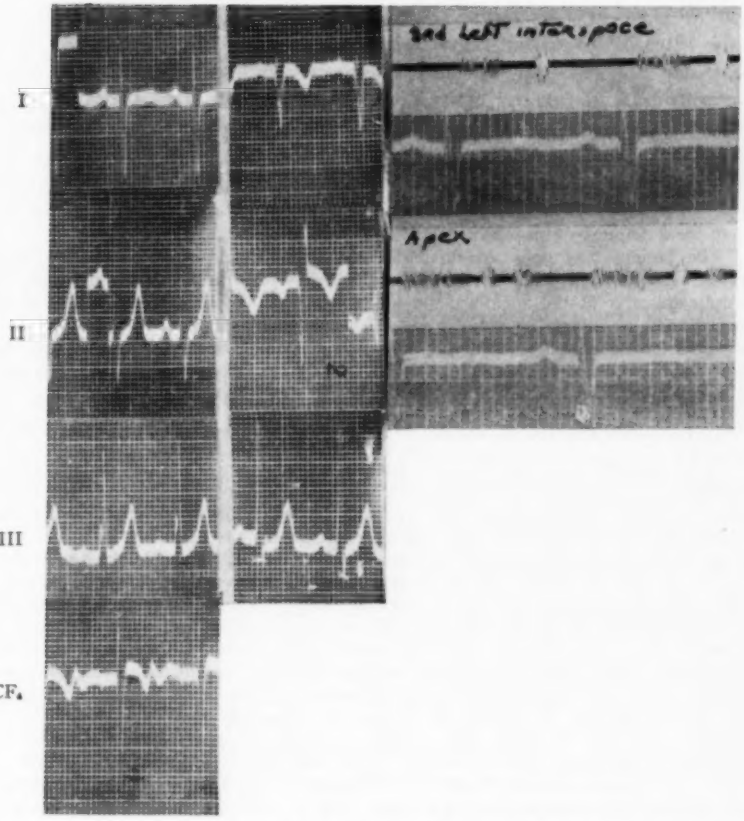

FIG. 6. The electrocardiogram in Case 10. The second column shows the unipolar limb leads aV-L, aV-R, aV-F. The third column shows a stethogram at the third left interspace with only a systolic murmur present. At the apex both systolic and diastolic murmurs are present.

poorly developed and nourished white male. The patient was underweight and smaller than normal for his age. He developed moderate dyspnea upon exertion. There was overaccessibility of the right ventricle with a systolic thrill felt along the left sternal border. The precordial thrust was quite marked and there was a slight asymmetry of the thoracic cage. At the apex a grade III systolic and diastolic murmur was heard. There was a systolic murmur along the left sternal border which was transmitted upward to end in a sharp P_2. The diastolic murmur could be heard only at the apex. Fluoroscopy showed an enlarged heart with increased pulmonary conus area and a marked hilar dance. A chest x-ray is shown in figure 5. The electrocardiogram and stethogram are shown in figure 6. The patient was catheterized and findings compatible with a patent ductus arteriosus were found.

	O_2 vol. %
S.V.C.	11.1
R.A.	11.95
R.V.	12.9
Pulmonary conus	13.9
Right pulmonary artery	14.25
Femoral artery	19.6

Though there was elevation of the oxygen content in the right ventricle, the larger increase in the pulmonary artery and clinical findings were considered sufficient for a diagnosis of a patent ductus arteriosus.

The patient was operated on February 4, 1948, and a large patent ductus ligated. Examination on February 22, 1948 showed a rapid heart rate but the diastolic murmur at the apex was no longer present. In the third and fourth left interspaces a systolic thrill and a grade III harsh systolic murmur were still present. Examination on February 25, 1948 showed the heart rate to be much slower and under fluoroscopy the marked hilar dance previously noted was not seen. The heart had not decreased in size. The systolic thrill and murmur were still present.

(*b*) *Patent Interatrial Septal Defect with Anomalous Pulmonary Vein.*

A 34 year old white female. The patient had whooping cough at the age of four at which time a murmur was first noted. Since then the heart murmur had always been present on examination. She was told to restrict her activities during high school. She had always been thin and never weighed more than 100 lbs. However, at age of 30 she started to gain to her present weight of 123 lbs. At the age of three months she had pneumonia, but no other serious illnesses except for a miscarriage in 1946. Her housework tired her after a few hours. There had been no chest pain but she did have exertional dyspnea and occasional palpitation. Her ankles were swollen at the end of the day. Physical examination revealed a short, well-nourished, dark female. The blood pressure was 130/80 mm. Hg. No clubbing or cyanosis was present. The radial pulse volume was diminished. The heart showed no enlargement by percussion. A systolic thrill was felt along the upper left border of the sternum. A grade IV harsh long systolic murmur was present over the second left interspace transmitted best to left but heard over entire precordium and into her back. The second pulmonic sound was accentuated. The lungs were clear. Fluoroscopy showed a somewhat enlarged cardiac shadow. The left main pulmonary artery was markedly dilated and pulsated vigorously. The aorta was hypoplastic and the right ventricle appeared enlarged. No deviation of the barium swallow was present. A circulation time with calcium gluconate was 12.5 seconds from arm to tongue. Her electrocardiogram showed marked right axis deviation. Catheterization studies revealed the following on several checks.

	O_2 content	O_2 saturation
S.V.C. 1.	13.46	70.7
2.	13.4	70.1
R. Aur. 1.	8.04	42.2
R. Vent. 1.	6.05	36.0
2.	6.15	36.4

The pulmonary artery could not be entered in this patient.

The significant difference between the right auricle and ventricle is consistent with an interauricular septal defect. However, the interesting finding is the high oxygen content of the superior vena cava. One explanation

for this is that one of the pulmonary veins empties into the superior vena cava. Brody in a review of the literature found that in all cases in which one or more of the pulmonary veins emptied into the right heart an associated patent foramen ovale was present.[30] This could account for the difference between the right auricle and right ventricle. However, the clinical findings also supported the diagnosis of interauricular septal defect. The patient was recatheterized two months later and similar results were obtained.

Discussion

Venous catheterization of the right heart has opened new possibilities for the recognition of many congenital defects, for elucidating the hemodynamic changes, and for assisting in rendering a prognosis by defining the nature and physiological magnitude of the defects. The utilization of this method in studying various other physiological alterations of the body has been mentioned. Finally, since certain varieties of congenital heart disease can be relieved by surgery, precise diagnosis is of such importance that all doubtful cases should be studied with all available diagnostic technics. The correct diagnosis of these anomalies and of others for which corrective surgical methods may be found in the future presents a real challenge to the clinician, the cardiologist, and the physiologist. Since the procedure of venous catheterization is quite safe, it can now be utilized in certain centers as a valuable diagnostic procedure.

Also, although criteria have been set up for the clinical diagnosis of a number of congenital cardiovascular anomalies, it should be remembered that as further anatomic studies are made these criteria may have to be changed. An example of this is the so-called "machinery" murmur that is associated with patent ductus arteriosus. This still constitutes the most characteristic feature of the physical findings but Cases 6, 9, and 10 of this present series are presented because they did not have this particular finding. Again in Cases 1 and 2, the characteristic signs of an interauricular septal defect were not present on physical examination. Many of these patients may have been previously misdiagnosed by ordinary methods. This is of particular importance in the armed services when the differential diagnosis of congenital heart disease versus other types of heart disease arises. Particularly is this true if compensation for life is concerned.

It is generally agreed that 50 per cent of patients with congenital cardiovascular anomalies have lesions that are considered clinically insignificant. However, accurate diagnosis should be made early in life. If surgery is to be considered, age is an important factor as children tolerate this type of surgery far better than adults.

Combined congenital cardiovascular lesions are more difficult to diagnose and evaluate, but with present day methods our diagnosis should become more accurate. Only patients with potentially cyanotic congenital heart disease have been presented. We will deal with the cyanotic group in a later communication.

SUMMARY

1. The procedure of cardiac catheterization is discussed.

2. Its value as a diagnostic aid in clinical studies has been stressed.

3. Twenty-five patients have had this procedure performed with no significant complications.

4. Ten patients in the potentially cyanotic class of congenital anomalies have been presented in detail.

5. One patient, Case 11, had the interesting anomaly in which one of the pulmonary veins empties into the superior vena cava.

6. One patient, Case 6, with a patent ductus arteriosus, had only a systolic murmur on auscultation, but a stethogram showed both systolic and diastolic murmurs. A second patient, Case 9, had only a systolic murmur present but a large patent ductus arteriosus was found at operation. A third patient, Case 10, had a systolic and diastolic murmur only at his apex with a patent ductus found at operation. The diastolic murmur disappeared after surgery.

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A PLAN FOR AVOIDING SENSITIZATION REACTIONS TO LIVER INJECTIONS *

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THE frequency with which intolerance to liver by injection occurs in practice cannot be readily estimated. Whenever it does arise, however, the problem which it presents may be of serious import to the patient and the satisfactory solution correspondingly gratifying. Delikat [1] found 14 of 200 patients intolerant to liver by injection. In some cases the reaction symptoms were alarming and required hospitalization.

The case to be reported and the measures employed may therefore be of interest since the literature gives the impression that the recognized approaches to the problem are often inadequate. This is very evident in the series reported by Feinberg, Alt and Young.[2] Clinical experience indicates that the sensitization is not specific to the animal species source of the extract but rather to the liver extract itself. A shift to a different animal source of the extract has not as a rule met with success. The usual approach, therefore, has been an attempt at desensitization, starting with a minimal parenteral dose and increasing the dose gradually in closely spaced successive injections until an adequate therapeutic dose is reached after which the injections are continued at that point every two to four weeks or less frequently as the particular patient may require. The frequency with which the earlier desensitizing injections are repeated varies. Wintrobe [3] suggests starting with 0.01 c.c., repeating the earlier injections every 15 to 30 minutes in gradually increasing dosage and arriving at a final adequate dosage by the end of a week or less after which two to four weeks or more may elapse between doses. Other clinicians have suggested similar plans. While temporary desensitization by such a procedure seems to succeed quite regularly, reactions seem prone to recur after the patient has returned for a period to the routine of two to four week interval injections.[4, 5, 6] The time-consuming desensitization process must then be repeated. Schwartz and Legere [7] have made use of the newer antihistamine preparations to avoid or mitigate the reactions; they had moderate success in some cases.

While the successful innovation here reported refers to a single case only, it seems reasonable to infer from the experience with this case that it would be successful in most if not all others.

CASE REPORT

The patient, Mrs. A. W., a widow, first consulted me on August 3, 1944 at the age of 69. She was the mother of seven healthy children; the past and family

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histories were otherwise irrelevant. For the previous seven years she had been treated with liver extracts by mouth (Lextron) after having had an initial course of liver injections. These were stopped because of "reactions." She found the constant taking of oral medication irksome, would occasionally allow the therapy to lapse and would then suffer loss of appetite and feel generally ill. She came to me first in one of these intervals. She was a well-preserved, well-nourished woman who did not appear ill. The positive findings were a basal systolic heart murmur and an impaired vibratory sense over both lower extremities. The patellar reflexes were present and equal. Gastric aspiration showed a histamine fast achlorhydria. She lived at a distance from St. Louis; frequent office visits were impractical. She was again returned to her liver-iron oral medication and urged to continue it faithfully. But when I saw her again on March 19, 1945 the blood picture was not satisfactory and she was given 1 c.c. of Reticulogen (Lilly). This was repeated for a time, at intervals of one to several weeks, along with the oral medication with good response. She was unable to return for further injection and, when next seen on October 8, 1945, the hemoglobin was down to 62 per cent (Sahli). She was again given 1 c.c. of liver intramuscularly. Fortunately she waited in my reception room to be called for by her daughter. Before the lapse of 30 minutes she was in an allergic reaction of rather alarming intensity: general flushing, facial edema, oppression in chest, coarse tremor, and a feeling of great restlessness. With suprarenalin hypodermically the attack subsided gradually in the course of two hours. She was told to increase her oral dosage by half, representing about 50 per cent above the usually accepted maintenance dosage. The hemoglobin rose to 85 per cent and the red count to 4 million and this level was maintained for a few months with the increased dosage but by April 8, 1946 the hemoglobin was again down to 60 per cent. An injection of 0.05 c.c. of liver was followed in a half hour by red, swollen hands but no severe reaction. During the course of the next week she was given frequent injections in gradually increasing dosage up to 1 c.c. which was tolerated without reaction. The interval between injections was increased to one and later to two weeks. After the third such two week interval the injection again produced a moderately severe reaction. The succeeding injection was preceded an hour by the administration of Benadryl but again was followed by reaction. The hemoglobin, however, was up to 94 per cent, the red count 4.39 million, and on September 27, 1946 she was placed on folic acid 5 mg. daily. On this dosage she maintained a constant level of hemoglobin and red cells and felt very well. She continued in this manner until July 1947 when she reported numbness and tingling of the fingers. The blood values remained unchanged. Oral liver in the usual full therapeutic dose was added to the folic acid administration; later the liver dosage was doubled. Despite this and the continuation of a satisfactory blood picture the paresthesias increased, walking became difficult, the vibration sense in the lower limbs was absent, pain and temperature sense dulled, patellar and Achilles reflexes absent. She was hospitalized and given a daily dose of liver extract (1 c.c. = 15 units) starting with .05 and increasing to a dosage of 0.8 c.c. There were no reactions. A daily dosage of 0.8 c.c. was continued for another two weeks with distinct improvement in the paresthesias. The patient's daughter was instructed in the use of the hypodermic and the patient was sent home on a regime of a 0.4 c.c. injection of liver every other day. This was later reduced gradually until a dosage of 0.25 c.c. every other day was reached on December 15. This dosage has been maintained to the time of this report (five and one-half months). The paresthesias disappeared slowly but completely. Of late the patellar reflexes can be elicited. They are weak but definitely present; the vibratory sense in the lower limbs remains absent. Repeated blood counts show a hemoglobin of 100 per cent or a little more and a red count hovering a little over 5 million.

Discussion

Reactions to parenteral liver therapy are not infrequently met. Oral administration may prove a suitable substitute but the literature and the case here reported bear witness that this alternative is frequently not adequate (Wintrobe, l.c.). The methods of desensitization by minute and gradually increasing dosage are effective but there seems to be general agreement that when the injections in therapeutically effective amount are again spaced to the usual two to four week intervals the sensitivity reactions soon reappear.

The parenteral injection of liver extract requires no more skill than the administration of insulin, a procedure which is looked upon as a commonplace and is without hesitation entrusted to the patient or some household companion. The same plan of home administration seems entirely reasonable for parenteral liver administration. A spacing of 48 hours between injections would seem to prevent the development of sensitization reactions. It may be found that an interval somewhat longer than 48 hours will also protect against reactions. The dosage at each injection can be gauged to the need of the individual patient. This plan appears to offer a safe and easily managed method of solving a troublesome dilemma.

Addendum: Since this paper was written a second case has been treated according to the same plan and with equally satisfactory result.

The patient, Mary S., a widow of 70, was first admitted to the hospital on April 21, 1943 with anemia and general anasarca. The anemia was found to be of typical hyperchromic type; characteristic sternal marrow, histamine fast achlorhydria.

With hypodermic liver therapy there was prompt reticulocyte response and during her seven weeks of hospitalization the red count rose from 1.8 million to 4.8 million with disappearance of the anasarca. She moved from St. Louis, was cared for by another physician who found it necessary to change to oral medication because of "reactions." Some half year later she again came under my care, continuing on oral therapy during 1944–45. In March 1946 I again instituted hypodermic liver injections. After the second injection she complained of nausea; the third injection was followed by nausea, persistent sneezing, and urticaria, and she refused further injections. She was again carried along on oral therapy with satisfactory results. On June 1, 1948 after an absence of two months she came to the office complaining of diarrhea, ankle edema, and weakness. She asserted that she had continued her medication without interruption. The blood showed a hemoglobin of 56 per cent; red cells 2.0 million, white cells 6,400; marked anisocytosis and poikilocytosis. The oral liver dosage was increased but after two weeks the symptoms and blood picture were essentially the same and she was hospitalized. She was given four to six hypodermic injections of liver (Reticulogen) daily starting with 0.05 c.c. with increments of .05 c.c. at each dose until a dosage of 0.6 c.c. was reached. There were no reactions. At the end of six days she was sent home with directions to have an injection of 0.25 c.c. of liver (Reticulogen) every third day. This has been continued to date (a period of eight weeks). No reaction has occurred, no urticaria, etc.: subjectively she was much improved. Her blood picture on June 21 showed a hematocrit reading of 27 per cent; red count 2.3 million, hemoglobin 7.8 gm. On August 13 the red count was 4.3 million, hemoglobin 15.3 gm. The smear showed a slight anisocytosis.

Both patients have continued in an eminently satisfactory condition and without sign of reaction 14 months and five and one-half months respectively after starting the regime of closely spaced fractional injections.

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THE CLINICAL ASPECTS OF COMPLETE AURICULOVENTRICULAR HEART BLOCK: A CLINICAL ANALYSIS OF 71 CASES *

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COMPLETE auriculoventricular heart block is a relatively rare complication of various types of heart disease. An analysis of the records at the University of Iowa Hospitals revealed 71 instances of this conduction defect, and a study of the records of these patients disclosed some interesting manifestations and variations from the usual clinical concepts.

The symptoms and physical findings of heart block, now commonly known as complete auriculoventricular heart block, were described many years before the advent of electrocardiography. Marcus Gerbezius,[1] who died in 1718, was perhaps the first to describe the slow pulse of heart block, but Morgagni [1] gave the first clear account in 1719. Adams' [1] account appeared in 1826, and Stokes [1] recorded his description in 1846. These early descriptions constitute the basis for referring to the syncope and convulsions that sometimes accompany complete A–V heart block as the Morgagni-Adams-Stokes syndrome.

Since the advent of electrocardiography, this conduction defect can be identified with certainty, and several significant reviews of the subject have been reported. In 1925 Willius [2] published a clinical analysis of 37 cases, which were independent of the action of digitalis and which he believed were due to disease of the auriculoventricular (His) bundle. Seven years later Ellis [3] analyzed a series of cases to ascertain the factors which govern the occurrence of symptoms and determine longevity. In 1936 Graybiel and White [4] published a report dealing with the clinical features of a group of 72 patients who revealed on at least one occasion complete auriculoventricular dissociation. An analysis of 64 cases, most of which were complete A–V block, was reported by Campbell [5] in 1944. This dealt particularly with prognosis, the incidence and significance of Stokes-Adams attacks, and the extent to which complete A–V block remains persistent or varies to partial or latent block.

The rarity of this conduction defect is evident from an analysis of consecutive electrocardiograms in the University of Iowa Hospitals. In a series of 25,286 tracings made from October, 1936, to January, 1948, there were only 69 patients with complete A–V heart block. White [6] found 79 instances in a series of electrocardiograms on 10,000 patients. Ellis [3] found it in only 40 of 7,515 patients having electrocardiograms. Partial auriculoventricular block and delayed auriculoventricular conduction are much more common.

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Etiology

Age: Patients of any age may have complete heart block but the incidence is much greater in later life. The age span in the present series was from 20 to 93 years, with the peak incidence in the eighth decade, the details of which are illustrated in figure 1. These figures are only slightly different from those reported in two comparable series by Campbell [5] and Willius.[2] Complete A–V heart block has been suspected in the fetus and confirmed electrocardiographically after birth. Thompson [7] reported two such cases, bringing

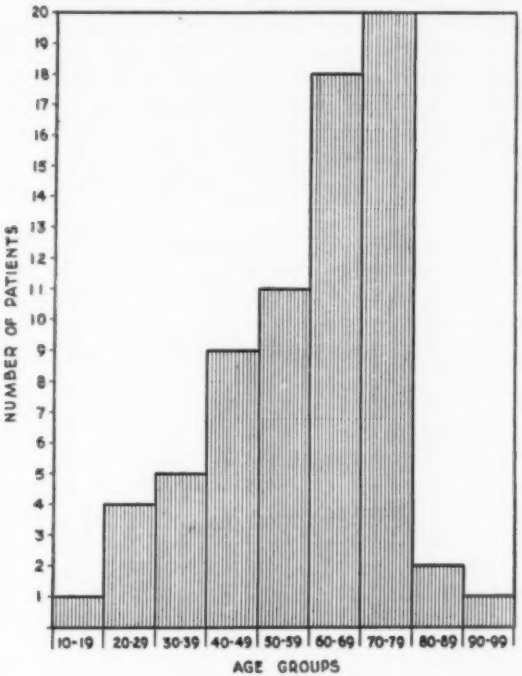

Fig. 1.

the total number of instances of complete heart block diagnosed antenatally to seven. A year later, in 1944, Hammond et al.[8] added another case in which a cesarean section was done because of beginning labor with an undilated cervix and a fetal heart rate of 40 per minute. An electrocardiogram on the fifth day after birth revealed a heart block with complete dissociation of the auricular and ventricular complexes.

Sex: It is generally agreed that complete A–V heart block is more common in males than in females, but there is some variation in the ratios.

There were 52 males and 17 females, a ratio of about three to one, in 69 of the patients in this series. There were twice as many males as females in three other series [2, 3, 4]; whereas, the ratio in Campbell's [8] patients was four to one. The ratio of two or three males to one female can be explained by the frequent association of complete A–V block and coronary sclerosis, a condition which is far more frequent in males.[9]

Causes

Hypertensive Vascular Disease and Coronary Sclerosis: The frequency with which complete A–V heart block is associated with hypertensive vascular disease and coronary sclerosis is well known, and the series reported in the literature suggests that coronary arteriosclerosis is responsible for the conduction defect in 50 to 75 per cent of all patients with complete A–V heart block.[3, 4, 5] In the present series there were 41 cases associated with coronary arteriosclerosis and its accompanying myocardial changes. Patients with hypertensive cardiovascular disease and acute myocardial infarction were included in this group.

Acute myocardial infarction was established clinically and electrocardiographically in eight patients and the diagnosis substantiated in five instances by necropsy. Although there was no special study to determine the anatomical relationship of the myocardial infarction to the conductive system, there was nothing to suggest that complete A–V block had existed before the acute myocardial episodes.

Complete A–V heart block is not a common complication of myocardial infarction. Graybiel and White [4] attributed the onset of only six of 72 instances to coronary thrombosis, while in other reports of complete heart block, myocardial infarction, coronary occlusion, or coronary thrombosis were not mentioned as causative factors.[2, 3, 5] In White's [6] series of 328 cases of myocardial infarction there was an incidence of only 3.6 per cent of auriculoventricular block, but the incidence of complete block was not specified. Levine [10] found only two instances in a series of 145 patients with coronary thrombosis, and in 1933 Ball [11] found only 15 instances in the literature and added one of his own.

Digitalis: It is well recognized that cardiac glycosides cause complete A–V heart block but lesser degrees of suppression of A–V conduction are much more common. When complete heart block results from these drugs it is a toxic manifestation.[6, 12]

Although it may be difficult to evaluate the relative importance of digitalis and the underlying heart disease in producing complete A–V heart block, it appeared that there were 12 patients in the present series in whom a digitalis substance was responsible. Each had received at least a sufficiently large dose over a long enough period of time to produce a complete digitalizing effect or, in susceptible individuals, an intoxication; complete block disappeared within eight days (average 5.2 days) after the drug was discontinued. It has been

shown that some of the effects of digitalis may persist on the electrocardiogram for as long as four weeks,[13] but no information was found in the literature regarding the duration of complete A–V block due to digitalis after the drug has been discontinued. The consistent time relationship of the disappearance of the conduction defect in these patients after withdrawal of the drug suggested a causal relationship. There is a wide variation in the frequency with which others have found digitalis intoxication the cause of complete A–V heart block.[3, 4, 5, 6]

Congenital Heart Block: The incidence of congenital complete heart block is uncertain. Jaleski and Morrison [14] reviewed the literature in 1942 and found only 80 cases. In a series of 1200 infants cited by Hammond et al.[8] there were 50 cases of heart block with only three listed as complete congenital block. These data suggest that this is a relatively rare cause of complete heart block, but Campbell [15] believes that congenital complete heart block is not rare but that it is overlooked because the ventricular rate is relatively fast and because the possibility is not borne in mind. He further emphasized that complete heart block of unknown cause in elderly patients may be a congenital form that has not been recognized.

With due regard to the pitfalls in establishing a clinical diagnosis of congenital complete A–V heart block, it was believed to be established with reasonable certainty in nine instances in the present series, an incidence which was similar to that of other series.[3, 4, 5] The criteria for this diagnosis included a history of slow pulse from early life, no history of any disease that could have been responsible for acquired complete A–V block, and electrocardiographic confirmation of the conduction defect. In some instances the heart block was associated with other signs of congenital heart disease.

Rheumatic Heart Disease: In discussions of complete A–V block, rheumatic heart disease is usually listed as a causative factor. Because of the frequency of prolonged PR intervals in the electrocardiograms of patients with acute rheumatic fever, it is easy to assume that complete A–V heart block is a fairly frequent complication. Yet, there were surprisingly few instances of this conduction defect in reports dealing with rheumatic fever, acute rheumatic carditis, or quiescent rheumatic heart disease.[16, 17, 18]

Two of the present series of patients had diagnoses of rheumatic pancarditis at necropsy. A third was a 30-year-old white female who had developed rheumatic fever within the preceding year and presented evidence of mitral stenosis. A fourth patient, 68 years old, gave a history of rheumatic fever at the age of 12 and insisted that the slow pulse dated from that illness. On the basis of these observations complete A–V block definitely appeared to be a manifestation of rheumatic heart disease in the first two patients and was probably of a similar origin in the last two patients.

Scarlet Fever: Scarlet fever is rarely complicated by complete A–V block. There were only two such instances in the present series. They have been reported previously by Paul and Rhomberg [19] who were unable to find similar

instances in the literature. Another case of complete A–V heart block associated with scarlet fever was reported by Davis and Smith,[20] but there were also manifestations of exophthalmic goiter which according to the authors predisposed to the acute infection and also to the secondary myocardial involvement which resulted in complete heart block.

Syphilis: Syphilis was the cause of complete heart block in only one patient in this series, a 49-year old male with aortic regurgitation, left ventricular hypertrophy, and strongly positive blood and spinal fluid serologic tests. The incidence of complete A–V block in syphilitic heart disease was also rare in some of the other reported series.[2, 3, 4, 5] However, in 1925 Willius [2] referred to several reports in the literature, and among 48 cases of complete A–V heart block accepted by Mahaim and Yater [21] as being satisfactory from the clinical and histopathologic standpoints, there were seven that were due to gumma of the interventricular septum with destruction of the A–V bundle.

Diphtheria: Diphtheria is a most important causative factor of complete A–V block but was not encountered in this series of patients. Ellis [3] found it as an associated factor in only one instance, and in another series of 37 cases it was encountered only twice.[2] Diphtheria was a questionable causative factor in four of 72 cases of complete A–V block reported by Graybiel and White.[4]

Complete A–V block is more common than partial heart block in diphtheritic myocarditis as was indicated in a review of all the reported cases of diphtheritic heart block by Massey and Walker.[22] It was found that 39 were partial and 59 were complete.

Hyperthyroidism: Hyperthyroidism was not an important factor in producing complete heart block in the present series. In 1933 Davis and Smith [20] reviewed the literature from 1882 and found only four such cases and added six of their own, but three of the patients reported by these authors had, in addition to hyperthyroidism, acute tonsillitis and a fourth had scarlet fever. In the other two patients that they reported there was reason to believe that the heart block was precipitated by the effect of digitalis on a previously injured A–V bundle. They discussed evidence indicating that hyperthyroidism predisposed these patients to the development of acute infections and also to secondary myocardial involvement which resulted in the occurrence of the heart block. It is difficult to be sure how important hyperthyroidism was in producing heart block in these patients.

Steuer,[23] on the other hand, reported a case which appeared to be due solely to hyperthyroidism, the block eventually disappearing after thyroidectomy. Aisner and Dorsey [24] reported another case which could be attributed to an overdose of thyroid extract, although uremia and pneumonia also existed. They suggested altered metabolism, the state of nutrition of the myocardium, and other factors as possibilities in the pathogenesis of complete A–V heart block in hyperthyroidism.

Complete A–V heart block also has been associated with neoplastic invasion of the conduction system,[25] uremia,[26] acute appendicitis,[27] pneumonia,[28] peritonitis,[28] and trauma.[29]

Clinical Picture

Symptoms: The symptoms of complete A–V heart block vary from transient episodes of mild giddiness to frequent and severe episodes of syncope and convulsions. Such symptoms are all due to cerebral anoxia, with the exception of palpitation which sometimes accompanies the forceful systolic thrust due to very slow ventricular rate. The writer agrees with Schnur [30] that the term Stokes-Adams disease has been best defined by Parkinson [31] as "a name applicable to patients with complete heart block who suffer from loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these." Undoubtedly the Stokes-Adams syndrome has received more emphasis than it deserves because its designation serves no useful purpose in the present state of diagnostic precision with electrocardiography except to imply that cerebral anoxia is severe enough to cause unconsciousness. Therefore, the patients in the present series were not classified according to whether or not they had this syndrome.

Only 25 patients in the present series had symptoms that were due to complete A–V heart block. Bizarre symptoms occasionally occurred that were apparently due to episodes of cerebral anoxia. The report of the following patient is illustrative:

Case 1. A 51-year-old farmer and coal miner was admitted to the University of Iowa Hospitals because of abdominal pain, headaches, and syncope. Seventeen months previously he had an attack of severe pain in his lower abdomen which was followed by a sharp frontal headache. The whole episode lasted only a few seconds but there was a similar spell later that day. After the onset of the symptoms the pulse was always slow. Ten months later another attack occurred which was similar to the first except that it was preceded by dizziness and weakness so severe that the patient fell to the floor. For the seven months before this admission to the hospital these episodes occurred several times each day. The past history was unimportant. On examination he did not appear to be ill but complained of episodes of pain that began in the lower abdomen and migrated to the forehead. These attacks were synchronous with periods of ventricular asystole which lasted about 10 seconds. Between these spells the ventricular rate was 24 beats per minute, the blood pressure was 160/70 mm. Hg, and the heart was slightly enlarged. There was a loud, rough, blowing systolic murmur that was easily heard over all the precordium. The examination of the abdomen was normal. An electrocardiogram, which is partially reproduced in figure 2, revealed an A–V heart block with a bundle branch type of ventricular pattern and periods of ventricular asystole which coincided with episodes of the symptoms. Ephedrine sulfate appeared to be effective in preventing the attacks.

Rate: The ventricular rates in this series were characteristically slow, but there were notable exceptions. They varied from two to 103 beats per minute with an average of 44.8. This average ventricular rate was some-

what faster than has usually been reported and may have been due to factors other than heart block. Of the four patients with ventricular rates above 70, three were in shock due to myocardial infarction, while the other was in severe congestive heart failure. The average ventricular rate was 42.6 beats per minute if these four patients are excluded from the series. Rapid ventricular rates in complete A–V heart block have been reported by others.[32]

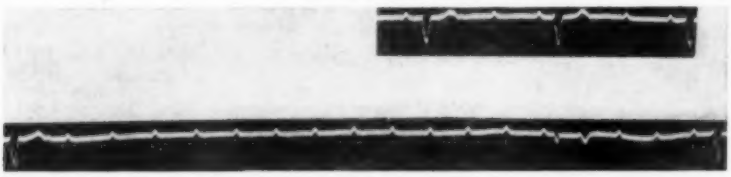

FIG. 2. Electrocardiogram showing ventricular asystole during an episode of symptoms in case 1.

Blood Pressure: It has been stated that there is a tendency toward an elevated systolic blood pressure and an increased pulse pressure when the ventricular rate is very slow.[6, 33] However, Ellis [3] found increased pulse pressures only in older age groups. On the basis of this observation and his earlier study [34] he believed that high pulse pressure in complete A–V block was usually related to peripheral arteriosclerosis.

TABLE I

Probable Causes of Complete AV Heart Block

Cause	Number of Patients
Coronary sclerosis and hypertensive vascular disease	41
Digitalis intoxication	12
Congenital	9
Rheumatic	4
Scarlet fever	2
Syphilis	1
Undetermined	2
Total	71

Table 2 does not indicate a significant relationship between wide pulse pressures and slow ventricular rates.* On the other hand, the average pulse pressure for patients over 40 years of age was 85.4 mm. (44 patients); whereas, the average pulse pressure for patients under this age was 52.9 mm. of mercury (nine patients). Assuming that there is more peripheral arteriosclerosis and atherosclerosis in patients in the older age groups, it appears that the findings in the present series support the studies and observations of Ellis [3] and Campbell [5] that these are the important factors in explaining

* This group is unselected except to exclude those patients who did not have blood pressures recorded when it was certain that they had complete A–V block and those in whom there were obvious factors other than complete block that affected the blood pressures, such as shock associated with myocardial infarction and hypotension associated with terminal stages of congestive heart failure.

TABLE II

The Relationship of Pulse Pressure to Ventricular Rate in Complete AV Heart Block

Ventricular Rate (Beats per minute)	Number of Patients	Average Pulse Pressure (mm. Mercury)
20–29	6	89.5
30–39	14	94.1
40–49	19	76.6
50–59	9	73.8
60–69	3	88.3
70–79	—	—
80–89	2	85.0
Total	53	

the increased pulse pressure in most of the patients with complete A–V heart block.

Associated Signs of Heart Disease: The importance of complete A–V heart block as a manifestation of serious heart disease was indicated by the frequency of associated signs of heart disease in this and in other series.[2, 3] Among the 59 patients in the present series in whom complete A–V block was not due to digitalis intoxication, 34 had enlarged hearts, six others had electrocardiographic and other clinical evidence of myocardial infarction, and two more had auricular fibrillation. Another had cardiac edema, and adhesive pericarditis was evident in one patient. Two of the remaining 10 patients had scarlet fever which was believed to be responsible for complete heart block.

Associated Electrocardiographic Findings: Associated electrocardiographic abnormalities were frequent. S–T segment shifts and T-wave abnormalities in the eight patients with acute myocardial infarction were sufficiently characteristic to suggest this diagnosis. Digitalis effect was also evident in the S–T segments as well as in the T-waves. Thus complete A–V block appeared to have no influence on the effect of myocardial infarction or the effect of digitalis on the electrocardiogram. There were 20 instances of auricular fibrillation which is a greater incidence than others have reported.[2, 3, 4] However, it is reasonable to expect this arrhythmia to be associated frequently with complete A–V heart block because it is also a manifestation of serious heart disease.

The problem of the interpretation of bundle branch type of ventricular complexes associated with complete A–V heart block is of special interest. In a theoretical discussion Horine and Weiss [35] emphasized the impossibility of being certain that complete A–V block and bundle branch block existed concomitantly when only one tracing was examined. On the other hand, they pointed out that a combined diagnosis could be made if there was bundle branch block as the only abnormality in a tracing and later another tracing on the same patient showed a complete A–V block with a similar bundle branch block pattern. They also believed that the same diagnosis was tenable if a patient with a complete A–V block exhibited a change from supraventricular to bundle branch block complexes. Katz [36] has indicated that the

interpretation of intraventricular block in combination with complete A–V block should not be made unless the former persists in electrocardiograms on the same patient when the A–V block is absent. Complete auriculoventricular heart block with bundle branch type of ventricular complexes in the electrocardiogram also has been attributed to bilateral bundle branch block lesions.[21, 37, 38]

The ventricular complexes were abnormal in the tracings of 26 of these patients. Eighteen were interpreted as left bundle branch block and eight as right bundle branch block.

Eleven of this group with bundle branch type of ventricular complexes had additional tracings in which complete A–V block was absent. In 10 of these 11 patients the bundle branch type of ventricular complexes persisted after the A–V block had disappeared indicating that there was a bundle branch block. In the other patient there was a change from a left to a right bundle branch block pattern when the A–V block disappeared. The latter patient may have had bilateral bundle branch block which caused A–V dissociation in the first tracing which changed to a unilateral branch block.

On the basis of the studies of others that have just been cited and our own electrocardiographic observations, it appears unjustified to interpret a single electrocardiogram which shows a combination of complete A–V heart block and bundle branch type of ventricular complexes as a complete A–V block with a bundle branch block lesion because of the other abnormalities of conduction that can cause the same pattern. Two such abnormalities follow: First, a block at the A–V node or in the main bundle of His in combination with a single pacemaker in one of the ventricles; second, bilateral bundle branch block with or without a defect in the main bundle of His or A–V node. Although Bain and others [21, 37, 38] have pointed out that bilateral bundle branch conduction defects are usually signified in the electrocardiogram by varying ventricular complexes in the presence of A–V heart block, ventricular complex changes may not appear in a single tracing.

It is suggested that an electrocardiogram indicating complete A–V heart block and bundle branch type ventricular complexes be identified as complete A–V heart block with abnormal intraventricular conduction instead of subscribing to the common practice of interpreting such patterns as complete A–V block with a bundle branch block.

Prognosis

The prognosis of patients with complete A–V heart block depends on the associated heart disease unless there are symptoms of cerebral anoxia. In series of unselected patients of complete heart block the average survival period is relatively short. Campbell [5] observed 34 patients with complete A–V block and found that they lived an average of two and one-half years. In another series reported by Willius,[2] the average length of life according to clinical histories was two and nine-tenths years with 15 years as the longest survival period.

Patients with congenital complete A–V block appear to live longer than those with other etiologic types. Campbell [16] reported such a series consisting of seven patients between the ages of 22 and 42 who were leading ordinary lives without trouble from their hearts. There are occasional patients living many years with complete A–V heart block which apparently was not congenital in origin.[39] One patient in our series may represent such an example.

Case 2. The patient was 69 years old and dated his slow pulse from an episode of polyarticular arthritis which occurred at the age of 12. There were no other symptoms until 10 years before admission to the University of Iowa Hospitals in December of 1946 after which time occasional Stokes-Adams attacks had occurred. The examination on admission indicated that the radial pulse was 28 per minute. There were no cardiac enlargement, murmurs, nor signs of cardiac failure. The electrocardiogram revealed a complete A–V dissociation with an auricular rate of 60 and a ventricular rate of 30.

It is possible that this patient had complete A–V heart block for 50 years as the only clinical manifestation of rheumatic heart disease.

When complete A–V block complicates diphtheria, the available information in the literature indicates that the prognosis is grave. Burkhardt, Eggleston, and Smith [40] reported 17 patients with conduction defects associated with diphtheria. The 11 of these who developed A–V dissociation all died. Wesselhoeft [41] indicated in an extensive review of cardiovascular disease in diphtheria that when injury to the musculature or conduction system fails to cause death at the time of the myocarditis, the tendency is to complete recovery, but added that rare cases of permanent complete A–V heart block are on record. White and Jones [42] cited a patient in whom complete A–V block persisted after the acute phase of the disease had subsided.

On the other hand, Stuyvesant and Levine [43] attempted to show that diphtheria in childhood was an etiological factor in the development of heart block in later years by comparing 14 cases of complete A–V heart block with a control series of 600 consecutive surgical patients. It was found that 50 per cent of the patients with heart block gave a past history of diphtheria; whereas, only 6 per cent of the surgical patients gave such a history.

Complete A–V heart block is rare in pregnancy.[44] However, it has been encountered, and patients have been allowed to continue a normal pregnancy with successful delivery.[45] Interruption of pregnancy in such patients should depend on factors other than the heart block, such as congestive failure and serious associated congenital lesions, unless symptoms due to the conduction defect are severe.

Treatment

It is necessary to treat complete heart block only when there are associated symptoms or when it is the result of the toxic effects of drugs, such as digitalis. In some instances complete A–V heart block can be ignored and therapy directed at other manifestations of heart disease.

There was specific management for complete heart block in only 21 patients or 29.6 per cent of the present series. The most important and effective measure was the withdrawal of a cardiac glycoside. There were 12 patients in whom complete heart block disappeared after a digitalis substance was discontinued, and a similar measure might have been life-saving in another. Paredrine, which has been reported to be more advantageous than ephedrine sulfate or epinephrine hydrochloride [46] was given to six patients to increase the ventricular rate. The ventricular rate was increased in two patients. In two other patients the drug was used in conjunction with the withdrawal of digitalis so the effect of paredrine was indefinite. In a fifth patient there was doubtful benefit, and in the last member of this group the administration of paredrine was accompanied by an elevation of blood pressure so the drug was discontinued. Two other patients who were treated for complete heart block appeared to get relief from epinephrine hydrochloride. But it must be pointed out that one of these epinephrine-treated patients also received digitalis to assure a permanent complete heart block in the hope of preventing episodes of ventricular asystole during shifts from incomplete to complete A–V block. The effect of epinephrine hydrochloride in this instance might be questioned.

Twenty-three patients did not receive treatment for heart disease. Twelve patients were treated for congestive heart failure. Seven were treated for myocardial infarction. Three patients with rheumatic fever and two others with scarlet fever were managed only from the standpoint of their systemic diseases. The records of three patients did not indicate clearly the types of treatment used.

In retrospect, the use of drugs to stimulate the ventricles may not have been appropriate in all instances in which they were used because some of the episodes of cerebral anoxia may have been caused by ventricular tachycardia or by ventricular fibrillation. That Stokes-Adams syndrome can result from these two mechanisms as well as ventricular asystole has been demonstrated adequately by Parkinson [31] and Schnur.[30] In spite of the prevailing opinion that quinidine is contraindicated in the presence of conduction defects, when there is graphic evidence that the symptoms of complete heart block are due to episodes of ventricular tachycardia or ventricular fibrillation it seems reasonable that the use of quinidine might be more effective than drugs that are known to increase ventricular irritability, such as paredrine, ephedrine sulfate, or epinephrine hydrochloride. Yet, in such a patient reported by Schnur [30] 132 grains of quinidine administered over a period of three days were ineffective. On the other hand, epinephrine effectively prevented Stokes-Adams attacks and the arrhythmias which precipitated them. The author indicated that one may surmise that the advantageous effect of epinephrine on the coronary flow more than compensated for its potential harmful direct effect on myocardial irritability.

Summary and Conclusions

A study of the clinical aspects of complete A–V heart block based on the hospital records of 71 cases and reports in the literature has been presented.

1. Complete A–V heart block is a rare conduction defect with the highest incidence in males over 40 years of age.

2. Complete A–V heart block complicated coronary sclerosis and hypertensive vascular disease in 41 cases, and it was the result of digitalis intoxication in 12 others. Other causal factors were less frequent.

3. There were symptoms in only 25 cases that were directly related to the heart block.

4. Evidence was presented to show that the wide pulse pressure in complete A–V heart block is more commonly related to peripheral arteriosclerosis and hypertensive vascular disease than to a slow ventricular rate.

5. The importance of complete A–V heart block was indicated by its frequent association with evidence of significant heart disease (51 cases) and digitalis intoxication.

6. The interpretation of a single electrocardiographic tracing with a combination of complete A–V heart block and a bundle branch type of pattern is discussed.

7. The prognosis depends upon the severity of the symptoms of complete A–V block and the associated heart disease.

8. Approximately one-third of the cases in the present series received treatment for complete heart block, another one-third for other manifestations of heart disease or a related systemic infection, and the remaining patients were not treated for heart disease.

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SODIUM SUCCINATE* AS A TEST OF CIRCULATORY EFFICIENCY†

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When Blumgart and Weiss [1] recorded their observations on the time required for radium to traverse a given portion of the circulatory circuit, an important advance was made in the study of the velocity of blood flow. Since then a large literature has grown indicating that other substances may be used to make similar observations. In the main, these agents lend themselves to division into two groups. In one group are those which give a subjective end-point. In order to determine the velocity of blood flow in this group, the observer must not only brief his patient adequately but must have his complete coöperation. The second group yields an objective end-point. In the former group, one finds decholin,[2] glucose,[3] calcium gluconate,[4] magnesium sulfate,[5] vitamin B,[6] and ether.[7] The latter group includes sodium cyanide,[8] paraldehyde,[9] lobeline,[10] histamine,[11] carbon dioxide,[12] fluorescein,[13] and papaverine.[14]

Sodium succinate was given intravenously to patients with peripheral vascular disease and coronary heart disease. It was observed that following the injection of a small amount of the solution, a cough or a paroxysm of three or four coughs resulted. In time this was followed by profuse vasodilatation. While investigating the latter reaction of the cardiovascular system to sodium succinate, its use as another means for measuring the velocity of blood flow was suggested.

Hussey and his co-workers [15] enumerated several requirements to be fulfilled by the agent used as a test of circulatory efficiency. They were as follows. It should be non-toxic. It should have no undesirable effects upon the condition being studied. The unpleasant side effects should be minimum. Elimination should be rapid so that the procedure could be repeated. The end-point should be recognized easily. Since all of these requirements were fulfilled by the solution under investigation, it occurred to the author that sodium succinate could be used to advantage as another agent to test the efficiency of the circulation. In the control group, patients with cardiac disease were excluded. The test was done as part of a routine physical examination.

Procedure

The patient was permitted to rest in the recumbent position for at least 15 minutes prior to the start of the test. There was no discussion of any

*The sodium succinate used in this experimental study was generously supplied by Brewer & Co. Inc., Worchester, Massachusetts. The author wishes to express his gratitude to Dr. Paul C. Barton, M.D., Medical Director of Brewer & Co. for his coöperation.

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phase of the procedure other than to announce to the patient that a circulation test was to be performed. In that way there was no interference on the part of the patient in arriving at the end-point. The patient was instructed to breathe normally and to relax. Assurance was given so as to allay anxiety and coöperation was requested.

The arm selected was abducted through an angle of approximately 45 degrees and was supported on an arm board so that the antecubital vein was at the level of the right atrium (approximately 10 centimeters above the plane of the back). A one and one-half inch, 19 gauge needle attached to a 2 c.c. syringe containing 1.5 c.c. of a 30 per cent aqueous solution of disodium succinate hexahydrate was introduced into the antecubital vein according to the usual technic for venipuncture. Following the release of the tourniquet, at least 15 seconds were allotted to permit the return of the venous flow to normal. Then the contents of the syringe were ejected as rapidly as possible. The time was measured with a stop-watch from the very beginning of the injection to the end-point.

TABLE I

Age Distribution—60 Cases—Control Group

Age Group	Number of Cases	Mean Circulation Time in Seconds
21–30	16	15.0
31–40	21	14.7
41–50	13	16.7
51–60	5	15.3
61–70	4	16.5
71–	1	16.0

OBSERVATIONS

The beginning of the end-point was indicated by an upward movement (simulating a swallow) of the cricoid cartilage and time was taken when this movement was observed. The sudden desire to swallow was attributed by the patients to sensations described as "a sudden tightening of the throat," "an acid taste," "a choking sensation," "a fullness in the throat," "a transient feeling of suffocation," and "a feeling of warmth in the throat." Very soon thereafter, there followed either a single cough or a paroxysm of three or four coughs. Within a very few seconds, usually approximately 20 seconds, the reaction had subsided and the patient made inquiry concerning the procedure.

Table 1 contains the age distribution of the control group of individuals. The patients were grouped into the decades as indicated. Most of them were between the ages of 21 years and 50 years. The circulation times were broken down into groups so that the mean circulation time in seconds could be recorded in each decade. It will be noted that there was no significant variation in the mean circulation time in the age groups studied. The mean circulation time for the entire group of 60 patients was 15.8 seconds. The extremes were between 12.0 seconds and 19.5 seconds.

Estimates of circulation time were made on 12 patients who were in congestive heart failure. The test was done before therapy was started and at intervals thereafter until compensation was restored. There were no untoward reactions in this group. They had no more discomfort as a result of the test than did the control group. The end-point was sharp and the cough subsided quickly without increasing the dyspnea already present as a result of the congestive heart failure. The results of the tests are recorded in table 2. It will be noted that the circulation time diminished as compensation was restored.

TABLE II

Circulation Time (in Seconds) in Cardiac Disease

Case Number	During Decompensation	After Therapy
1	21.5	16.7
2	24.0	19.4
3	24.0	20.3
4	28.0	22.0
5	32.0	20.0
6	23.4	20.2
7	21.0	17.3
8	25.4	20.6
9	27.4	20.3
10	25.0	18.4
11	26.0	18.5
12	24.0	16.8

There were no unpleasant side reactions following the injection of sodium succinate in either group of patients.

SUMMARY

1. The velocity of blood flow was determined in a group of 60 patients without cardiac disease. In this group the mean circulation time was found to be 15.8 seconds.

2. Similar estimations were made in a small group of cardiacs in congestive heart failure prior to institution of therapy and after compensation had been reëstablished.

3. Since no untoward reactions followed the use of this agent and since the requirements enumerated above are fulfilled, sodium succinate is suggested as another agent for the estimation of the velocity of blood flow.

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PROPYLTHIOURACIL IN THE TREATMENT OF ANGINA PECTORIS: A COMPARISON WITH THIOURACIL THERAPY *

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The effectiveness of thiouracil in the treatment of the anginal syndrome was first described by Raab [1] and Ben-Asher [2] in 1945. Clinical improvement was obtained in seven of 10 patients treated by Raab and in eight patients treated by the author. The following year DiPalma and MaGovern [3] emphasized the disadvantages of thiouracil in the treatment of angina pectoris. They found, however, that the precordial pain was beneficially affected at least for a period of time in four of their eight patients. In the same year Reveno [4] described eight patients with angina pectoris treated with the drug. Improvement was noted in five patients. Two patients did not improve and one who showed evidence of improvement was not studied long enough to permit classification of result. Ben-Asher,[5] in 1947, reported the results of treatment with thiouracil in 37 patients with angina pectoris. Improvement was noted in 25 patients.

The occurrence of toxic reactions to thiouracil was found to be a serious deterrent to its use in angina pectoris as in hyperthyroidism. In a search for substances which would eliminate these disadvantages, Astwood, Bissell and Hughes [6] found that of the many compounds they tested in animals, propylthiouracil possesses most antithyroid properties. This drug was used successfully by Astwood and VanderLaan [7] in 100 patients with hyperthyroidism without any significant ill effects.

The purpose of this paper is to present data regarding the use of propylthiouracil in patients with angina pectoris and to compare the results with those obtained with thiouracil therapy.

Method

The procedure used in this study was in the main similar to that described in a previous communication.[5] In the early period of this investigation when the effects of the drug and the optimum dosage were not known, the initial daily dose of propylthiouracil was 75 mg. given by mouth in the form of 25 mg. tablets every eight hours. When it became apparent that this initial dose was too small and that the drug rarely causes ill effects, the dosage was increased to 150 or 200 mg. The initial daily dose was given for a period

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† Dr. Ben-Asher died on April 27, 1949.

of two to five months after which the patient was placed on a maintenance dose of 25 to 50 mg. for a period varying from seven to 10 months. In order to eliminate the possibility of suggestion, the course of treatment was interrupted in some patients by a placebo. The placebo consisted of tablets which looked like propylthiouracil in size and shape.

The patients were instructed to continue their previous activities if possible, and to report at each visit (1) the number of anginal attacks experienced, (2) the severity and duration of each attack, (3) the amount of physical activity before the attack occurred, and (4) the number of nitroglycerine tablets used since the last visit.

In order to obtain objective data, standardized exercise tolerance tests as described by Master,[8] were performed before treatment and at frequent intervals during this study. This consisted of ascending and descending a two-step staircase and noting the number of ascents necessary to induce substernal or precordial discomfort. Each test was made at least two hours after a light meal, in a room the temperature of which was maintained between 72° and 74° Fahrenheit.

The results were classified as excellent, good, fair and poor according to the criteria which follow. The results were regarded as excellent if (1) the patient did not experience any precordial distress in the course of normal activities, (2) there was an increase of 100 per cent or more in the exercise tolerance test. The results were regarded as good if (1) mild pain occurred infrequently, (2) there was an increase of at least 100 per cent in physical activities, (3) there was an increase of at least 50 per cent in the exercise tolerance test. The results were regarded as fair if (1) there was an increase of 50 per cent in the normal physical activity before the occurrence of pain. (2) there was an increase of 25 per cent in the exercise tolerance test. The results were regarded as poor when these criteria were not met.

Results

A total of 32 patients, 25 men and seven woman varying in age from 40 to 70 years, were treated with propylthiouracil. The duration of angina ranged from six months to 10 years. Ten patients had a history of myocardial infarction. Fourteen patients had previously received thiouracil. Nine of these had had a relapse after cessation of thiouracil therapy. In five the thiouracil was discontinued because of toxic reactions.

Seven patients received an initial daily dose of 75 mg. of propylthiouracil. In these patients the dose was later increased to 150 mg. Twenty-five patients received an initial dose of 150 mg. daily. In 12 of these the dose was increased to 200 mg. per day.

The results are shown in table 1. Twelve of the 32 patients (37.5 per cent) thus treated showed clinical improvement. Twenty patients did not respond to treatment. The onset of improvement occurred within two to

TABLE I

Results in 32 Patients with Angina Pectoris Treated with Propylthiouracil

Case No.	Name	Age	Sex	Duration of Angina Pectoris	Degree of Angina Pectoris	Blood Pressure	B.M.R.		Initial Daily Dose (mg.)	Onset of Improvement (Wk.)	Duration of Treatment (No.)	Results	Remarks
							Before Treatment	Maximum Change Under Treatment					
1	E. T.	44	M	15 mo.	4+	140/90	+3	−4	75 increased to 150	—	9	poor	Status unchanged with treatment.
2	M. L.	69	F	2 yr.	3+	180/100	−8	−6	75 increased to 150	—	10	poor	Anginal pain less severe.
3	S. A.	70	M	2 yr.	3+	170/110	+17	−16	75 increased to 150	6	10	good	Fever with thiouracil. None with propylthiouracil. Improvement maintained 12 wk. after drug was stopped.
4	W. R.	59	M	30 mo.	4+	130/80	+21	+6	75 increased to 150	8	9	fair	Fever with thiouracil. None with propylthiouracil. Relapse 2 weeks after drug was stopped.
5	A. G.	67	F	2 yr.	2+	160/90	+7	−2	75 increased to 150	—	11	poor	Status unchanged with treatment.
6	F. N.	67	F	2 yr.	2+	180/106	+3	−5	75 increased to 150	—	9	poor	Good result with thiouracil.
7	M. C.	49	M	4 yr.	2+	140/80	−5	−9	75 increased to 150	—	9	poor	Fair response with thiouracil; neutropenia in fourth month. No change with propylthiouracil.
8	M. R.	52	F	5 yr.	3+	190/100	+16	+7	150 increased to 200	—	7	poor	Status unchanged with treatment.

TABLE I—*Continued*

Case No.	Name	Age	Sex	Duration of Angina Pectoris	Degree of Angina Pectoris	Blood Pressure	B.M.R.		Initial Daily Dose (mg.)	Onset of Improvement (Wk.)	Duration of Treatment (No.)	Results	Remarks
							Before Treatment	Maximum Change Under Treatment					
9	S. S.	62	M	8 yr.	4+	200/100	−4	−6	150 increased to 200	3	10	poor	Temporary improvement. Relapse while under treatment.
10	S. V.	42	M	3 yr.	2+	120/80	+8	−17	150	2	9	fair	Improvement maintained 12 weeks after propylthiouracil was stopped.
11	J. H.	50	M	2 yr.	3+	120/80	+9	−13	150	2	9	good	Relapse when course was interrupted by placebo. Relapse 4 weeks after propylthiouracil was stopped.
12	H. B.	60	M	4 yr.	2+	160/90	−8	−9	150	—	6	poor	Died of cerebral hemorrhage in seventh mo. of treatment.
13	M. J.	47	M	15 mo.	2+	150/80	+3	+4	150 increased to 200	3	10	fair	Relapse when course was interrupted by placebo. Relapse soon after propylthiouracil was stopped.
14	H. F.	45	M	6 mo.	4+	130/70	−5	−16	150 increased to 200	—	8	poor	Status unchanged with treatment.
15	M. L.	51	M	30 mo.	3+	160/100	+2	+5	150 increased to 200	4	10	fair	Fair result with thiouracil. No change with placebo. Relapse 3 weeks after propylthiouracil was stopped.
16	J. S.	42	M	1 yr.	4+	170/80	+7	—	150	—	2½	poor	Died of coronary occlusion in third month of treatment.
17	E. C.	48	M	7 yr.	3+	140/80	+1	−9	150	2	10	good	Excellent result with thiouracil. Relapse soon after propylthiouracil was stopped.

TABLE I—*Continued*

Case No.	Name	Age	Sex	Duration of Angina Pectoris	Degree of Angina Pectoris	Blood Pressure	B.M.R.		Initial Daily Dose (mg.)	Onset of Improvement (Wk.)	Duration of Treatment (No.)	Results	Remarks
							Before Treatment	Maximum Change Under Treatment					
18	M. R.	60	M	2 yr.	3+	140/80	−5	−16	150 increased to 200	—	12	poor	Fair result with thiouracil.
19	E. A.	52	M	8 mo.	2+	160/100	+14	+9	150	3	11	good	Relapse when course was interrupted by placebo. Relapse soon after propylthiouracil was stopped.
20	D. C.	50	F	1 yr.	4+	170/90	+6	+8	150	—	8	poor	Status unchanged with treatment.
21	M. H.	61	M	3 yr.	3+	190/100	+9	−7	150	2	9	good	Fever with thiouracil. None with propylthiouracil. Relapse soon after propylthiouracil was stopped.
22	E. P.	50	M	4 yr.	3+	160/90	+6	+5	150 increased to 200	—	8	poor	Good result with thiouracil.
23	L. G.	45	M	2 yr.	4+	120/80	+5	+4	150 increased to 200	3	10	fair	Good result with thiouracil. Relapse soon after propylthiouracil was stopped.
24	S. R.	44	M	30 mo.	2+	130/70	−8	−9	150 increased to 200	—	9	poor	Excellent result with thiouracil.
25	J. R.	60	M	1 yr.	2+	150/90	+17	−13	150	3	9	good	Relapse when course was interrupted by placebo. Relapse 6 weeks after propylthiouracil was stopped.
26	F. Y.	58	M	10 yr.	3+	168/90	+16	+9	150	—	9	poor	Fever with thiouracil. None with propylthiouracil.

TABLE I—*Continued*

Case No.	Name	Age	Sex	Duration of Angina Pectoris	Degree of Angina Pectoris	Blood Pressure	B.M.R.		Initial Daily Dose (mg.)	Onset of Improvement (Wk.)	Duration of Treatment (No.)	Results	Remarks
							Before Treatment	Maximum Change Under Treatment					
27	J. L.	41	M	15 mo.	2+	144/76	−2	−1	150	—	7	poor	Status unchanged with treatment.
28	E. F.	52	F	8 mo.	4+	200/120	+9	+11	150	—	9	poor	Anginal pain less severe.
29	M. R.	41	M	2 yr.	3+	130/80	+7	−18	150 increased to 200	2	10	good	Relapse when course was interrupted by placebo. Improvement maintained 14 weeks after propylthiouracil was stopped.
30	H. G.	49	M	2 yr.	3+	180/90	−6	+1	150 increased to 200	—	10	poor	Good result with thiouracil.
31	J. D.	60	M	2 yr.	2+	140/80	+3	+4	150 increased to 200	—	12	poor	Anginal pain less severe.
32	H. R.	64	F	3 yr.	2+	190/100	−8	−5	150	—	10	poor	Good result with thiouracil.

eight weeks. The average was 3.3 weeks. The duration of treatment ranged from seven to 12 months. The average was 9.3 months. Of the 12 patients who improved, the results were regarded as good in seven and fair in five. In none of the patients who showed clinical improvement was the result classified as excellent. One patient (case 9) was free of anginal attacks for six weeks and had an increase of 120 per cent in the exercise tolerance test after two months of 150 mg. of propylthiouracil. A relapse occurred while on a maintenance dose of 50 mg. When the dose was again increased to 200 mg., this patient still experienced frequent anginal attacks, although they occurred less often and were less severe than before treatment. One patient (case 16) died of a coronary occlusion in the third month of treatment and another (case 12) died of a cerebral hemorrhage in the seventh month of treatment. Of the nine patients who had had relapses after thiouracil was discontinued only three showed improvement with propylthiouracil. One patient (case 24) in whom the result was classified as excellent with thiouracil, did not show any improvement with propylthiouracil. The result in another patient (case 17) regarded as excellent with thiouracil, was classified as good with propylthiouracil. Relapses occurred in five of six patients in whom the course of treatment was interrupted by a placebo. Relapses also occurred within three months after treatment was stopped in nine of the 12 patients who showed clinical improvement.

Effect on the Basal Metabolic Rate

Before treatment the basal metabolic rate varied from — 8 to + 21 per cent. The average was + 3.9 per cent. With propylthiouracil therapy the range was between — 17 and + 11 per cent. The average was — 3.3 per cent. Six patients who had no symptoms of hyperthyroidism had a control basal metabolic rate of over + 10 per cent. Four of these improved with propylthiouracil. The basal metabolic rate was depressed below — 10 per cent in seven patients during treatment. Five of these improved with treatment. There was no significant depression of the basal metabolic rate in seven of the 12 patients who responded to propylthiouracil therapy. Two patients (cases 14 and 18) in whom the basal metabolic rate was depressed below — 15 per cent did not show any clinical improvement.

Effect on the Blood Cholesterol

Table 2 gives the result of blood cholesterol determinations on 15 patients before and during treatment. The control blood cholesterol varied from 166 to 219 mg. per cent. The average was 191.3 mg. per cent. With treatment the blood cholesterol ranged from 183 to 274 mg. per cent. The average was 209.2 mg. per cent. An appreciable rise in the blood cholesterol was noted in three patients. The maximum increase was 76 mg. per cent (case 10). This increase paralleled the fall in the basal metabolic rate from + 8 to — 16

TABLE II

Effect of Propylthiouracil on the Blood Cholesterol
(Mg. Per Cent)

Case	Before Treatment	Maximum Change With Treatment
4	186	195
7	174	190
8	210	226
10	198	274
13	176	172
17	205	216
18	176	229
19	206	188
23	189	183
25	184	228
26	166	186
28	188	194
29	192	208
30	218	230
32	202	219

per cent. The blood cholesterol was not significantly altered in 12 of 15 patients who were treated with propylthiouracil.

Figure 1 shows the relationship between the blood cholesterol, basal metabolic rate and the clinical response in the 12 patients who improved with propylthiouracil. A definite decrease in the average number of daily attacks and an increase in the average number of ascents was noted in the first month of treatment. The basal metabolic rate was not changed. With continua-

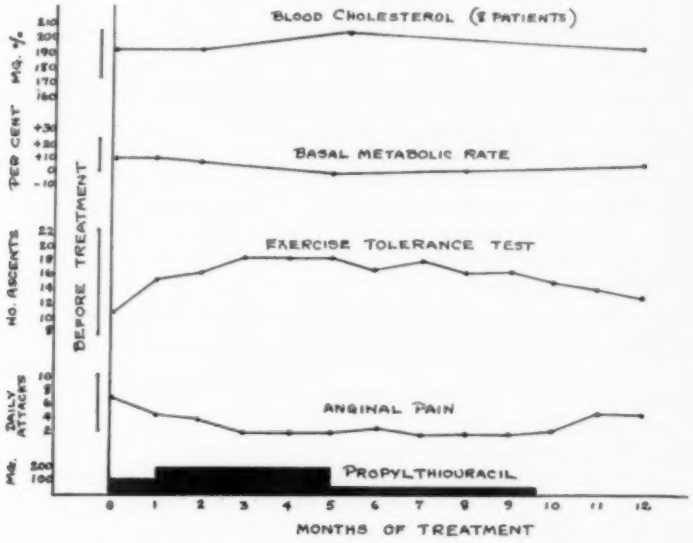

FIG. 1. The relationship of anginal pain and exercise tolerance test to basal metabolic rate and blood cholesterol in 12 patients.

tion of treatment the basal metabolic rate was slightly decreased and the blood cholesterol was slightly increased. The effect on the precordial pain and the exercise tolerance was considerably greater. Within three months after propylthiouracil was stopped, the precordial pain was increased and the number of ascents was diminished. The basal metabolic rate and the blood cholesterol returned to control levels.

Side Effects With Propylthiouracil

No toxic reactions were encountered as a result of treatment with propylthiouracil. Four patients who developed a fever with thiouracil in the first 10 days of treatment, did not show any rise in temperature with propylthiouracil. One patient (case 7) who had neutropenia in the fourth month of thiouracil treatment did not have any change in the white cells with propylthiouracil. Pruritus associated with urticarial rash was noted in two patients treated with propylthiouracil. The drug was not stopped and the rash disappeared spontaneously.

DiPalma and MaGovern [3] described pulmonary edema with nocturnal and exertional dyspnea which they attribute to the use of thiouracil in a patient treated for angina pectoris. This complication was not encountered in this series. One patient (case 19) who had dyspnea and wheezing during sexual intercourse did not have this complaint while under propylthiouracil treatment.

Comparison of Results of Therapy With Thiouracil

A comparison of the results of treatment with thiouracil is shown in table 3. Twelve of the 32 patients (37.5 per cent) improved with an initial daily dose of 150 to 200 mg. of propylthiouracil in contrast to 25 of the 37 patients (67 per cent) who improved with an initial daily dose of 0.4 to 0.6 gm. of thiouracil. The degree of response with propylthiouracil was also less than that obtained with thiouracil. Relapses in the first three months after cessation of treatment occurred in five of the 25 patients (20 per cent) who responded to thiouracil and in nine of the 12 patients (75 per cent) who improved with propylthiouracil. The average depression of the basal metabolic rate was 24.3 per cent with thiouracil and only 7.2 per cent with propylthiouracil. The average rise in the blood cholesterol was 81.6 mg. per cent with thiouracil and 17.9 mg. per cent with propylthiouracil therapy. Treatment was stopped in eight patients treated with thiouracil because of toxic reactions. Treatment was not discontinued in any of the patients treated with propylthiouracil because of ill effects.

Discussion

It is evident from these studies that propylthiouracil is not as effective as thiouracil in the treatment of angina pectoris. The effect of the former drug

on the basal metabolic rate and on the blood cholesterol is considerably less than that of thiouracil. Toxic reactions, however, occur less frequently with propylthiouracil therapy.

The fact that the circulation is influenced by the activity of the thyroid gland has been demonstrated both clinically and by experimental investigations. Long before the effects of a depression of the metabolic rate were observed clinically, it was found experimentally that animals exhibit an increased resistance to severe anoxia when their metabolism is depressed. As early as 1918, Streuli [9] reported that thyroidectomized rats withstand exposure to oxygen-want produced by a reduction of the atmospheric pressure better than normal animals. He also showed that splenectomy increases the sensitivity of rats to oxygen deficiency and that it also nullifies the bene-

TABLE III

Comparison of Results of Therapy in Patients With Angina Pectoris With Propylthiouracil and Thiouracil

	Propylthiouracil (0.4–0.6 gm.)	Thiouracil (150–200 mg.)
Total number of patients treated	32	37
Number of patients improved	12 (37.5%)	25 (67%)
Result: Excellent	None	7
Good	7	13
Fair	5	5
Poor	20	12
Duration of treatment (average number of mo.)	9.3	5.5
Onset of improvement (average number of wk.)	3.3	3.4
Number of patients with relapse within 3 months after drug was stopped	9 (75%)	5 (20%)
Average decrease in B.M.R. (per cent)	7.2	24.3
Average increase in blood cholesterol (mg. per cent)	17.9	81.6
Number of patients with side reactions	2	8
Number of patients in whom treatment was stopped because of toxic reactions	None	8

ficial effects of thyroidectomy. Duran,[10] in 1920, found that rats fed with thyroid substance show an increased sensitivity to anoxia. Houssay and Rietti,[11] in 1932, reported that thyroid extract and anterior pituitary substance increase the sensitivity of animals to oxygen deficiency. Barach, Echman and Molomut,[12] in 1941, found that thyroidectomized rats show a remarkably increased resistance to low barometric pressure, as well as to low oxygen concentration. The majority of thyroidectomized rats survived three weeks in a chamber kept at 6 per cent oxygen, whereas a similar percentage of normal rats died when exposed to the same oxygen concentration in 12 to 36 hours. In 1944, Gordon, Goldsmith and Charipper [13] reported that rats treated with thiourea for 12 days survived a reduction of atmospheric pressure to 200 mg. of Hg, whereas the majority of untreated control animals succumbed. In the same year, Leblond [14] confirmed the observation that thyroidectomy and thiourea increase the resistance of the rat to anoxia and that thyroxin decreases the resistance of the rat to anoxia. Hughes and Astwood,[15] also in the same year, reported that the administration of thiouracil to rats for six days increases the resistance to anoxia produced by low

barometric pressure and to low oxygen tension at atmospheric pressure. These authors suggested the use of this drug to improve the efficiency of aviators at high altitudes. In 1945, Goldsmith, Gordon and Charipper [16] presented additional evidence that thiourea and thiouracil are effective in increasing the resistance of rats to lowered atmospheric pressure. These results are in accord with the results obtained clinically with thyroidectomy and with antithyroid compounds in angina pectoris, a condition in which an inadequate supply of oxygen to the myocardium is present under certain conditions.

An explanation for these clinical and experimental observations requires consideration of the theories for the mechanism of pain production in angina pectoris. It is the belief of Levine and Eppinger [17] and also of Raab [1] that the thyroid gland sensitizes the heart to adrenalin. Anginal pain, Raab states, is caused by an increased concentration of adrenalin in the heart muscle which has been sensitized by the thyroid hormone. This author found that thyroxin sensitizes the heart of the rat to adrenalin and that pre-treatment with thiouracil reduces the sensitivity.[18] DiPalma and Dreyer,[19] on the other hand, found no antagonistic effect to epinephrine from thiourea in the cat and rat. Riseman, Gilligan and Blumgart [20] also reported that patients with angina pectoris, except those with severe myxedema were not more sensitive to the intravenous injection of a known concentration of epinephrine than were patients with no evidence of cardiovascular changes.

Another theory is advanced by Lewis [21, 22] who believes that the stimulus for pain in angina pectoris is the same as in intermittent claudication. From observations on the effect of exercise after arresting the circulation in the normal limb, Lewis, Pickering and Rothschild [23] conclude that pain in intermittent claudication is determined by a chemical or physiochemical stimulus developed in the muscle during its exercise. This stimulus they call Factor P. When a muscle contracts, changes such as a release of metabolites occur within its fiber but act outside the fibers in the tissue spaces. When muscular contraction occurs in the absence of blood flow, the metabolites, or Factor P, accumulate in the tissue spaces providing the stimulus for pain production. When muscular contraction occurs in the presence of blood flow, Factor P cannot rise to the corresponding level in the tissue spaces. Katz [24] also believes that the stimulus for pain in angina pectoris is a metabolic product, either lactic or phosphoric acid, formed during the catabolism of muscular activity. In a study of the amount of exercise required to cause pain and fatigue in the muscles of the arms of normal subjects, Katz, Linder and Landt [25] conclude that the pain results from the accumulation of the pain-producing substance(s) which is the product of muscular activity. This substance(s) is non-volatile, and appears to be acid in character. The appearance of pain in muscle, they conclude, is dependent not only upon the local production of pain producing substance(s) but is due to a certain extent upon the transport of these substances from other regions. As a

result of these investigations, Katz believes that a pre-pain stage exists in angina pectoris in which the metabolic product causing pain is increased in amount but not sufficiently to stimulate the pain end-organs. Pain will result when this substance reaches a concentration above the threshold of the pain end-organs. The accumulation of metabolic substances depends upon the amount of work performed by the heart and the coronary blood flow. When the coronary circulation is adequate these substances are either oxidized or diffused into the blood stream. When the coronary circulation is slowed or the amount of oxygen is decreased, the concentration of these chemical products will increase to provide the stimulus for pain production. It is significant that Gessell and his associates [26] found that the blood level of lactic acid was raised under conditions of anoxia. In the light of the above, the thiouracil compounds by inhibiting the formation of the thyroid hormone could diminish the concentration of the metabolites below a critical threshold of the pain end-organs.

It is unlikely that the action of the thiouracil compounds is limited to the thyroid gland. There is evidence [27, 28, 29] to indicate that these drugs act by the inhibition of the enzyme systems. In in vitro experiments, Warren [30] found that the respiration of rabbit bone marrow and exudate cells is inhibited by thiouracil. From studies on sea urchin egg development, Bevelander [31] concluded that thiourea causes inhibition of the enzyme systems which are necessary for the growth of the sea urchin. It is therefore possible that the thiouracil compounds may inhibit the formation of metabolites in the heart muscle itself. This may be accomplished either through their action as antioxidants by the depression of the enzyme systems or by some mechanism other than that of the inhibition of enzymes. That the formation of metabolites can be inhibited by a chemical substance may also be deduced from the experiments of Lundsgaard.[32, 33, 34] This investigator demonstrated that the formation of lactic acid in muscle can be prevented by mono-iodoacetic acid, and that this does not interfere with muscular contraction. Propylthiouracil may therefore decrease the concentration of metabolites in the heart muscle below the threshold of the pain end-organs independently of its antithyroid action. This would explain the beneficial results obtained in some patients with angina pectoris treated with the drug in whom no depression of the basal metabolic rate was noted.

1. Thirty-two patients with angina pectoris were treated with an initial daily dose of 150 to 200 mg. propylthiouracil. The results are compared with those treated with an initial daily dose of 0.4 to 0.6 gm. thiouracil.

2. Propylthiouracil, in the dosage used, is not as effective as thiouracil in the treatment of angina pectoris. Twelve of 32 patient (37.5 per cent) improved with the former drug as compared with 25 of 37 (67 per cent) who improved with thiouracil. Seven patients were symptom-free with thiouracil. There were no symptom-free patients with propylthiouracil.

3. Relapses after treatment was stopped occurred more frequently and earlier with propylthiouracil therapy.

4. The effect on the basal metabolic rate and the blood cholesterol was considerably less with propylthiouracil than with thiouracil.

5. The drug was stopped because of toxic reactions in eight patients (21 per cent) treated with thiouracil and in none of the patients treated with propylthiouracil.

6. Improvement may be obtained in some patients with angina pectoris with propylthiouracil without modification of the thyroid function. A possible explanation of these results is presented.

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CASE REPORTS

ROENTGEN THERAPY OF CUSHING'S SYNDROME (PITUITARY BASOPHILISM): REPORT OF A CASE OBSERVED FOR ELEVEN YEARS *

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Since Cushing's [4] original description in 1932 the syndrome of pituitary basophilism has become a well recognized entity. It is an uncommon disease which occurs more frequently in females than in males. The manifestations of the syndrome are painful obesity limited chiefly to the face, neck, shoulders and abdomen, thin reddish skin with purplish striae, acrocyanosis, hypertension and arteriosclerosis, kyphosis and backache with osteoporosis frequently resulting in multiple compression fractures of the vertebrae, weakness, amenorrhea in women, impotence in men, hirsutism without other evidence of virilism and hypoglycemia. The significant laboratory findings according to Albright [1] are an unresponsive alimentary hyperglycemia, insulin resistance, and a moderate increase in 17-ketosteroid excretion. Recently, an excessive output in the urine of 11-oxycorticosteroids has been demonstrated in patients with this condition.[3, 15]

It is now known that precisely the same clinical syndrome may occur in association with tumors of the adrenal cortex or in simple adrenal cortical hyperplasia without actual tumor. In the case presented here an exploratory laparotomy was performed early in the course of the disease to investigate the adrenal glands. No evidence of disease or abnormality was found in either adrenal gland and it must be assumed, therefore, that the classical syndrome described above and present in this case is the result of involvement of the hypophysis alone.

There is considerable controversy in the literature as to the value of irradiation of the pituitary in Cushing's syndrome.[2, 5, 20] Grant [9] remarks in summarizing the literature on roentgen therapy that of the three types of adenomas now recognized, the basophile adenoma is the most susceptible to this treatment, next the acidophile and lastly the chromophobe. He noted that cystic adenomas were less responsive to x-rays than the solid type. In his opinion, roentgen therapy as a primary therapeutic measure is indicated in all pituitary adenomas, solid or cystic. He found that if subsequent surgical intervention were done the procedure was not rendered more difficult because of previous roentgen therapy. According to his statistics, postoperative roentgen treatment seemed to prolong the period before evidence of recurrence of the adenoma appeared. These opinions were shared by Sosman,[18] who makes the statement that one should try irradiation in all cases of pituitary adenomas before resorting to surgical intervention. The latter author also stated that following irradiation satisfactory

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remission of symptoms and signs will be obtained in 50 per cent of patients with chromophobe adenomas, in 90 per cent of chromophile adenomas and in the majority of basophile adenomas.[17]

Thompson and Eisenhardt [20] in endeavoring to follow all reported cases of Cushing's syndrome indicated that roentgen treatment had failed in the majority of cases. They believe that if one course of well-planned irradiation proves unsuccessful, surgery should be attempted. In their review, out of 18 patients treated with irradiation, only one experienced temporary improvement. Dyke and Davidoff [6] report no definitely beneficial results in three recorded cases.

There are on record several striking instances of complete remission of the disease following irradiation of the hypophysis. Cushing's [4] patient had a remission lasting over 11 years. Jamin's [10] patient, a boy 14 years old with all the signs of the syndrome, completely recovered following irradiation to the pituitary. Ellman and Vilvandre [7] and Luft [14] report favorable results. It is interesting to note that Lisser [13] observed a case in which partial hypophysectomy alone was done without benefit of other therapeutic measures. The patient had a complete remission of symptoms for one year after which a relapse occurred with recrudescence of most of the features of the disease. At this time, roentgen therapy was ineffectual.

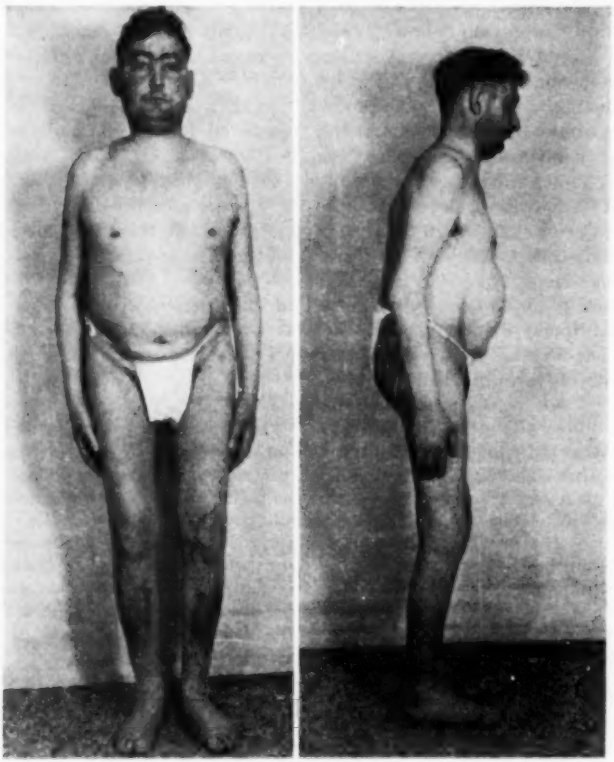
The case reported here is unique in that until there was recurrence of symptoms, the primary therapeutic measure was irradiation directed to the pituitary. The case has been followed over a period of 11 years and gives us the opportunity to evaluate this form of treatment.

Case Report

A 23 year old white male was first seen at the State of Wisconsin General Hospital on March 23, 1937, with the following pertinent signs and symptoms: backache, headache, gain of 30 lbs. in three months with the obesity confined entirely to the lower face (moon facies) and trunk especially over the shoulder girdle, breast and upper thorax (buffalo distribution); acrocyanosis, purplish striations on abdomen, loss of four inches in height, constricting sensation in thorax, loss of body hair, progressive weakness and fatigue, photophobia, inability to stand straight or work (figure 1). There was hypertension with the blood pressure recorded as high as 200/150 mm. Hg. retinal sclerosis, plethoric complexion and exquisite tenderness of the skin. Laboratory findings revealed diminished sugar tolerance, normal blood count, nonprotein nitrogen was 28 mg. per cent, basal metabolic rate minus 9, blood calcium 10.4 mg. per cent, blood phosphorus 3.8 mg. per cent, and blood phosphatase was 2.6 Bodansky units. Roentgenograms of the skull, spine and long bones revealed generalized osteoporosis of all the bones with compression fractures of the fifth and tenth thoracic and lower four lumbar vertebrae due to the marked demineralization (figure 2). The sella appeared normal at first but later examinations made in 1938 revealed definite enlargement of the left side giving a double contour to the floor and dorsum and considered consistent with a tumor in this area. Visual fields showed no gross abnormality despite an 11 year history of polyuria and polydipsia suggesting pituitary disease.

At the time of his first admission, the patient received a series of x-ray treatments to the pituitary region. This consisted of 4 × 100 r to the right and left temporal and glabellar regions through a 4 cm. × 4 cm. portal, 50 cm. FSD, HVL of 1.05 mm. Cu. A second similar series was given in May, 1937 and in June, 1937 the series was repeated using 150 r to the same three portals. No change was noted in the patient's signs or symptoms.

In August, 1937 the patient was admitted to the hospital and a laparotomy was done to rule out abnormality of the adrenal glands. Both adrenals were found to be normal in size and shape and without evidence of hyperplasia as well. The patient became somewhat more depressed mentally. He was nervous and irritable and for a time was confined because of suicidal intentions. Pain in his back was controlled partially by x-ray therapy to his spine, 3 × 150 r, 15 cm. × 15 cm. portals, 50 cm. FSD, HVL = 2.4 mm. Cu. In addition a fourth series of x-ray therapy was administered to



a *b*

FIG. 1*a* and *b*. Frontal and lateral views taken in March 1937 at the time of first admittance to the hospital. These show the characteristic adiposity of the lower face and trunk, striations on the abdomen and stooped posture.

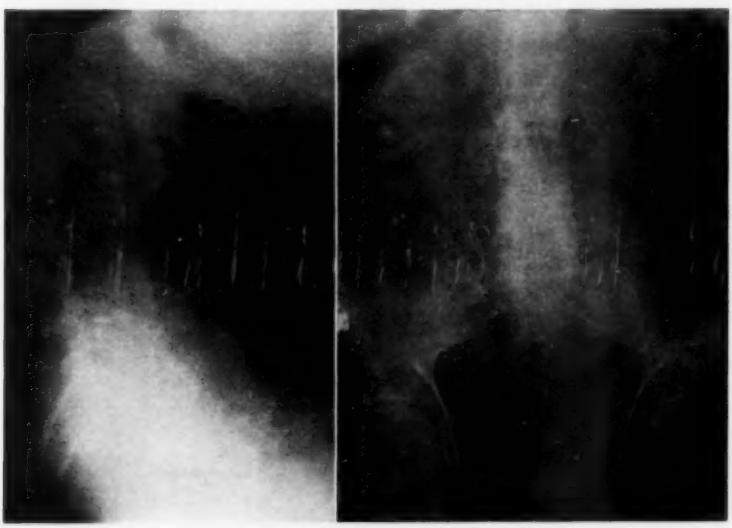
the pituitary area through right and left temporal portals, 6 × 100 r, HVL = 1.05 mm. Cu. He was given a Taylor brace as a support to his spine and left the hospital slightly improved.

Between October 1937 and August 1941, this patient was admitted to the hospital on nine different occasions. During this four year period there was steady improvement in his symptoms. In January, 1938 the patient was seen at the University of Chicago Clinics and received a fifth series of x-ray treatments to his pituitary gland

consisting of 6 × 300 r through right and left temporal and bregmatic areas, 50 cm. FSD, 7.5 cm. × 7.5 cm. portals. No further roentgen therapy was given until the present date (1948).

Until 1946, the patient had a complete remission of symptoms (figure 3). He gained strength, lost 25 pounds in weight and even worked as a farmer and as a section hand on a railroad. Roentgenograms of the skull and spine showed considerable recalcification of all of his bones and no further change in the sella.

In 1946 he suddenly developed weakness of his right lower and upper extremities; this was diagnosed as a stroke by his local physician. He then had a rapid return of all of his previous symptoms including the painful adiposity, progressive weakness, plethoric appearance, headache, and backache. In December, 1947 he received a sixth series of treatments to his pituitary area, 8 × 150 r, three 4 cm. × 4 cm. portals,



a *b*

FIG. 2*a* and *b*. Antero-posterior and lateral roentgenograms of the lumbar spine and pelvis showing the severe generalized osteoporosis of all of these bones associated with multiple compression fractures.

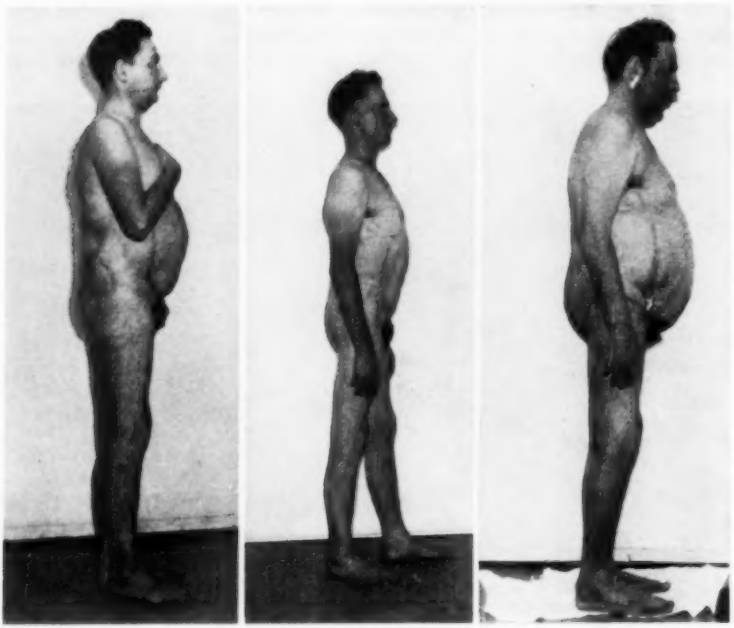
HVL = 1.05 mm. Cu. He was discharged on January 13, 1948 without much improvement. He received daily injections of testosterone and was given potassium citrate as well as a low sodium diet.

On February 24, 1948, a right frontal craniotomy was performed and an hypophysectomy attempted. Grossly, at operation, the contents of the sella turcica were not increased in amount but the material removed was heterogeneous in appearance, definitely granular, darker and more speckled than normal anterior lobe. There was no evidence of adenoma. The microscopic examination revealed only fibrosis and atrophy of the anterior lobe of the pituitary. The patient had an uneventful postoperative course but showed no definite change in his symptom-complex.

On April 1, 1948, a repair of an abdominal incisional hernia was attempted. The wound failed to heal and the patient's condition declined rapidly. Secondary infec-

tion of the operative wound occurred; *Clostridium welchii* was isolated from the area; there was rapid elevation of nonprotein nitrogen and creatinine and on April 15, the patient died.

At postmortem examination the pathologic findings were many. There was a postsurgical necrotic defect of the anterior abdominal wall together with gas gangrene of both legs. Of particular interest was the presence of diffuse enlargement of both adrenal glands with their weight being more than twice that of the normal. No adenomas were present and the histologic section showed diffuse areas of hyperplasia



a *b* *c*

FIG. 3*a* and *b*. Lateral views taken two and four years respectively after initial examination showing progressive improvement in posture and loss in abnormal adiposity. *c*. Appearance 11 years later after recrudescence of symptoms.

of the cortical cells with an increase in lipoidal content particularly in the zona reticularis and the zona fascicularis. The tissue remaining in the sella turcica again showed atrophy and fibrosis with little recognizable normal gland. Other postmortem findings were: recent infarction of the left ventricle of the heart with occlusion of the anterior descending coronary artery; occluding emboli in the right upper pulmonary artery and in both iliac veins at their junction with the inferior vena cava.

COMMENT

Several interesting facts are brought out in this case. In the first place, there is general agreement by all who were concerned in the care of this patient that irradiation of the pituitary was the only effective agent in bringing about remis-

sion for a period of about eight years. We may conclude, therefore, that radiation therapy can produce beneficial effects in Cushing's syndrome. Secondly, we wish to emphasize that improvement did not occur after the first series of x-ray treatments but definite response to treatment was noted after the fourth series. After the fifth series, the symptoms regressed to the point where further treatment was no longer indicated. This is in accord with the statements made by Kerr and Cooper [11] and by Sosman [18] who have emphasized the importance of giving adequate dosage in cases of pituitary adenomas. Sosman has remarked that the poor results in Cushing's cases which were irradiated were due to insufficient treatment. We have revised our own opinion as well and are using higher dosages in these cases. It is important, however, to avoid the opposite extreme and overtreat the pituitary area to the point of producing irreversible brain damage.

Kerr [5, 12] in a recent paper indicated that he treats his patients with a large amount of radiation administered in one course. He uses four portals, two temporal, a frontal and a vertical. The physical factors are 200 KV, HVL = 1.95 mm. Cu, 50 cm. distance and a 5 cm. cone. One hundred roentgens are given to one field the first day. If there is no reaction, two fields receive 100 r each the second day and thereafter 200 r are administered to each of two fields per day. A total of 2,000 r measured in air is delivered to each field.

As a sidelight, it is interesting to note that this patient had an excessive output in his urine of 11-oxycorticosteroids while the level of excretion of 17 ketosteroids was quite low. This is in agreement with the opinions expressed by Albright [1] and Gordon,[8] who have noted these changes in Cushing's syndrome where the major abnormality is in the pituitary gland while the adrenals are intact. They have stated further that the osteoporosis as well as the cutaneous manifestations are the result of a marked loss of protein. The demineralization of bone is due to inadequate tissue framework for the deposition of calcium and phosphorus compounds rather than an active withdrawal of calcium and phosphorus from the bones.[16] These facts fit in well with the case presented here where normal calcium and phosphorus levels were present in spite of the marked demineralization of the bones.

The presence of fibrosis and atrophy of the pituitary gland as noted at the time of hypophysectomy and at postmortem examination is evidence of the ability of roentgen irradiation to eliminate hyperfunction of this gland. It is conjectural but reasonable to assume that the recrudescence of symptoms in this case may have been due to the development of compensatory hyperplasia of the adrenal glands.

Summary

1. A brief review of the current literature of Cushing's syndrome is given with special consideration of the therapeutic aspect.

2. An illustrative case observed for 11 years is presented in which the primary therapeutic measure was irradiation of the pituitary gland by roentgen-rays.

3. We feel that this case proves the value of roentgen-rays as an important agent in the treatment of Cushing's syndrome. The clinical course as well as the findings at autopsy support this contention.

4. We are emphasizing the importance of using adequate dosage in these cases if good results are to be expected.

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SICKLE CELL ANEMIA AND CARCINOMA OF THE BREAST COMPLICATED BY PREGNANCY*

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THE literature contains records of pregnancy complicating sickle cell anemia in only 21 patients. This combination is therefore sufficiently rare that an additional case is in itself worth reporting. Besides sickle cell anemia and pregnancy,

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the patient we are reporting had carcinoma of the breast, and eventually died of metastatic lesions nine and one-half months after radical mastectomy. To the best of our knowledge, no patient has been previously reported with this unusual combination of diseases.

Sickle Cell Anemia and Pregnancy. In 1941, Kobak, Stein, and Daro [1] reviewed the existing literature on sickle cell anemia and pregnancy and added six cases of their own, making a total of 17 cases. These authors found the outlook poor for both the mothers and the babies. One-third of the women died during or shortly after pregnancy, and one-sixth of the pregnancies ended with the delivery of macerated fetuses. Furthermore, abortions were much more common than in normal women, and the incidence of preëclamptic toxemia and puerperal sepsis was unusually high. In 1943, van der Sar [2] published the case of a 26 year old Negress with sickle cell anemia who was observed through two pregnancies, one of which resulted in the birth of a living child. Spivack [3] in 1945 reported a pregnancy in a 35 year old Negro woman with sickle cell anemia which also resulted in the birth of a living child. This was the eldest patient with sickle cell anemia and pregnancy recorded, none over 30 years of age having been previously reported. The next case was that of a 32 year old Negress reported by Noyes [4] in 1946. This patient developed preëclamptic toxemia in the seventh month of pregnancy and died. The last case was that of Grover,[5] of a 17 year old patient with sickle cell anemia who developed a severe abdominal crisis when seven and one-half months pregnant, and delivered a stillborn child. All writers on the subject agree that fertility is impaired in women with sickle cell anemia and that pregnancy is very rare in these patients. Furthermore, when pregnancy does occur, it has an unfavorable effect on the course of the disease. Blood transfusion is the only treatment of value as far as the anemia is concerned.

Carcinoma of the Breast and Pregnancy. The combination of carcinoma of the breast and pregnancy is, like that of sickle cell anemia and pregnancy, a very bad one. According to Geschickter,[6] pregnancy has an unfavorable effect on carcinoma of the breast regardless of whether it was present before pregnancy began or developed during pregnancy or lactation. Carcinoma of the breast metastasizes earlier in the pregnant than in the non-pregnant woman. The axillary lymph nodes were involved in every case seen by Geschickter. None of the 15 patients reported by him who were operated upon for mammary cancer during pregnancy survived the five year period, and he states that permanent cure of a patient with carcinoma of the breast developing during pregnancy has not been recorded. Harrington's [7] experience is similar to Geschickter's. In reviewing all cases of carcinoma of the breast treated surgically at the Mayo Clinic between 1910 and 1933, he found no five year survival in pregnant women with carcinoma of the breast and axillary lymph node metastases at the time of operation. However, the outlook was somewhat better in a small group of similar cases without lymph node metastases. The increased estrogenic hormone in the blood of the pregnant woman has been considered an important factor in increasing the rate of growth of a breast carcinoma during pregnancy. This increase is at its maximum during the first half of pregnancy, since during the latter half the excessive estrogen is partially neutralized by the increased amounts of luteal hormone. The question of therapeutic abortion in patients with carcinoma of the breast should be considered, to remove this stimulating

effect of increased estrogenic hormone. However, to be effective abortion should be done in the first half of pregnancy.

Case Report

A Negro woman 28 years old was admitted to the Radiological Department of the Philadelphia General Hospital on April 18, 1946 because of a mass in the left breast. She was about seven and one-half months pregnant, and had been referred from the pre-natal clinic to the radiological out-patient clinic. A punch biopsy of the tumor in the left breast done on April 12 showed carcinoma, probably ductal in origin. The patient said she first noticed the mass at least nine years before. About March 1, when she was six months pregnant, it began to enlarge and become tender, and she developed pain in the left axilla.

Her past medical history showed that she had been unusually healthy for a patient who later proved to have sickle cell anemia. The only childhood diseases she recalled were mumps and chicken pox. She had one living child, nine years old, whose health she said was good. The present pregnancy was her second. Her last menstrual period began September 1, 1945. Her menstrual history prior to this had been normal. Her family history showed nothing of note, save that one of her six brothers had heart trouble.

Physical examination showed that the patient was well developed and somewhat obese, weighing 167 pounds. Her weight before she became pregnant was 150 pounds. Her blood pressure was normal, 122/70 mm. of mercury. No abnormalities were noted on examination of the heart or lungs. In the left breast, there was retraction of the nipple medially and superiorly. A hard irregular sharply demarcated tumor about 2.25 by 2.5 inches in diameter was present just medial to the nipple. There was puckering of the skin over the mass. In the left axilla there was a firm lymph node about 1.5 by 1 inch in diameter. In the abdomen the uterus was enlarged to a size consistent with a seven and one-half months pregnancy. Fetal heart sounds were not heard, but fetal movements were felt.

A chest roentgenogram taken before admission on April 11, 1946 was negative. Blood count on the day of admission showed hemoglobin 10.5 grams, 68.3 per cent; red blood cells 3,740,000; white blood cells 12,100 with 78 per cent polymorphonuclears, 20 per cent lymphocytes, 1 per cent eosinophiles, and 1 per cent monocytes. No sickle cells were noted on stained smear. However, a hanging drop preparation of the blood was not done at this time as sickle cell anemia was not suspected. Table 1 shows the initial and subsequent blood counts, and also lists the blood transfusions which were given to the patient. The blood Kline test was negative, and urinalysis showed nothing abnormal.

On April 19, 1946, left radical mastectomy was done by one of us (J. C. H.) under cyclopropane anesthesia. Pathologic diagnosis of the tumor was pregnant breast with medullary carcinoma and lymph node metastasis. During the operation the patient received 500 c.c. of compatible blood of type O which had been previously cross-matched. Her condition was good when she left the operating room.

Next day, April 20, 1946, she showed a rising temperature and cardiac rate. Fetal movements were not felt at this time, nor were fetal heart sounds heard. Chest x-ray showed a mottled density in the right lower lung field thought to be due to a pneumonic process. However, it seems likely that the pathologic process was pulmonary infarction from a pulmonary thrombosis, which is of course a common complication of sickle cell anemia. Sulfadiazine was started in the usual dosage of 1 gram every four hours after an initial dose of 3 grams. Next day her condition was worse, and she was placed in an oxygen tent. In addition to sulfadiazine, penicillin was started, 25,000 units every three hours intramuscularly. Blood count showed a leukocytosis of 47,650, and many sickle cells were seen on the stained smear. The diagnosis of sickle cell

anemia was confirmed by a hanging drop preparation of the blood. On April 23 she was delivered of a dead macerated fetus. She was given a second transfusion of 500 c.c. of blood on April 24. Next day she was sufficiently improved that she was comfortable outside of the oxygen tent. Her temperature and cardiac rate were only slightly elevated at this time. The sutures were removed from the incision the same

TABLE I

Summary of Blood Counts and Blood Transfusions

Date	Hemoglobin	Red Blood Cells (in millions)	White Blood Cells (in thousands)	Differential Count (%)	Comment
4/18/46	10.5 gm. 68.3%	3.74	12.1	P. 78, L. 20, E. 1, M. 1	No sickle cells noted on smear.
4/19/46					Transfusion 500 c.c.
4/21/46	13 gm. 84.4%	4.23	47.65	P. 89, L. 10, M. 1	Many sickle cells on smear and in hanging drop.
4/22/46	7.5 gm. 48.8%	2.37	39.0	P. 74, L. 16, M. 9, E. 1	Normoblasts and sickle cells on smear.
4/24/46	8.0 gm. 51.3%	2.51	18.5	P. 98, L. 2	Many sickle cells on smear. Transfusion 500 c.c.
5/9/46	8.5 gm. 55.3%	2.58	6.2	P. 77, L. 19, M. 2, E. 1, B. 1	
6/5/46					Transfusion 500 c.c.
6/10/46	9.5 gm. 61.7%				
12/27/46	10 gm. 64.9%	3.35	21.7	P. 66, L. 30, M. 4	Transfusion 200 c.c.
12/48/46					Transfusion 300 c.c.
1/9/47	7.5 gm. 48.8%	1.99	19.8	P. 65, L. 30, M. 2, E. 3	Many sickle cells and nucleated Rbc's on smear. Transfusion 500 c.c.
1/17/47	8.5 gm. 55.3%	2.52	11.9	P. 70, L. 26, M. 4	
1/27/47					Transfusion 500 c.c.
2/1/47	7.5 gm. 48.8%	1.99	36.0	P. 86, L. 8, M. 6	Nucleated Rbc's and sickle cells on smear.
2/3/47					Transfusion 500 c.c.

day, April 25. Two days later it was noted that there was some gaping of the wound margins with wound infection.

Her condition continued to show improvement until April 30, 1946. She was out of bed that morning when she suddenly screamed, became disoriented and extremely dyspneic, and went into shock. This episode was followed by a temperature rise to 103° F. and expectoration of bloody sputum. Physical findings later were compatible with a diagnosis of pulmonary thrombosis with infarction of the right lower lobe.

She was again treated with oxygen and again improved. Penicillin was discontinued on May 5, and sulfadiazine on May 7. A third blood transfusion of 500 c.c. was given on June 5. By June 9, chest x-ray was negative, with no evidence of metastases to lungs, ribs, or pleurae. By July 13, the wound infection had improved sufficiently that Thiersch and pinch grafts were done under local anesthesia. She was discharged to out-patient care on July 26, 1946.

She was followed in the out-patient clinic until her second hospital admission on December 26, 1946. On September 9, she complained of pain in the lumbar region of her back. However, x-ray of the entire spine showed no evidence of metastasis. On September 26, it was noted that the operative site was entirely healed. Her general condition was good, and she weighed 154 pounds. Chest x-ray on December 9 was again negative.

She was readmitted to the hospital on December 26, 1946 complaining of pain in the right upper quadrant of the abdomen, fever, sweating, and nervousness. These symptoms had begun about a week before admission. She appeared acutely ill with temperature 101° F., pulse rate 100 per minute, and respiratory rate 28 per minute. However, her nutrition was still good. Moderate icterus of the sclerae was present. There was no evidence of recurrence of the tumor in the operative site or in the left axilla. A soft mitral systolic murmur was noted on examination of the heart. The liver was enlarged to three fingers'-breadth below the costal margin, and extended beyond the mid-line into the left upper quadrant. It was firm, not tender, and did not feel nodular.

Blood count on December 27 again showed moderate anemia and leukocytosis (table 1). The icterus index was 30 units. Urinalysis was negative on admission, but later albuminuria was present in amounts ranging from 2 plus to 4 plus. She was given a blood transfusion of 200 c.c. on December 27, and of 300 c.c. on December 28. She continued to run a fever to 104° F., and the jaundice increased. On January 7, 1947 the icterus index was 95 units and the total serum bilirubin was 14.5 mg. per cent. Her blood urea nitrogen at this time was 55 mg. per cent, and she became confused and disoriented. By January 8, 1947 she again had findings in the base of the right lung suggesting pulmonary infarction. Oxygen therapy was again needed, and she was given penicillin, 25,000 units intramuscularly every three hours. Another blood transfusion of 500 c.c. was given on January 9. Subsequently she improved, with clearing of her sensorium and a drop in her temperature to normal. On January 21, x-ray of the skull, upper extremities, lungs, pleurae, ribs, and femurs showed no evidence of metastases. There was an area of osteosclerosis involving the descending portion of the right ischium. The nature of this was indefinite but the radiologist thought it could be an osteoblastic type of metastasis.

Her condition remained fairly good until January 26, when her temperature rose to 101° F. She was given 500 c.c. more of blood on January 27. She continued to go downward, however, and by February 3 she was irrational, her jaundice had deepened, and her liver was more enlarged. Although it was realized that the hepatomegaly and jaundice were probably due to metastatic lesions rather than to sickle cell anemia, she was given another blood transfusion of 500 c.c. on February 3. Her condition grew steadily worse. On February 8, her blood urea nitrogen was 144 mg. per cent and her plasma carbon dioxide was 25 volumes per cent. She died at 6:30 a.m. on February 9, 1947.

The important findings at necropsy * were as follows: The liver was enormous, weighing 4,140 grams, and extending well into the left hypochondrium. It consisted of innumerable white nodules which on microscopic section showed metastatic adenocarcinoma with extensive necrosis. Metastatic carcinoma was also found in the lumbar and thoracic vertebrae, and in the right ilium. The spleen was very small,

* We are indebted to Dr. A. Valdes Dapena for the autopsy findings.

as is often the case in adults with sickle cell anemia, weighing only 24.5 grams, and showed microscopically siderofibrotic replacement of the pulp.

Discussion

Sickle cell anemia was not diagnosed in this case until late in pregnancy, and after radical mastectomy done for carcinoma. It is of interest that there was nothing in the history to suggest sickle cell anemia prior to this time, and that the patient had a living child nine years old. Furthermore, none of the usual physical signs of sickle cell anemia were present. We believe that this patient had only latent sickle cell anemia until the additional burden of pregnancy or carcinoma of the breast or both made the disease clinically active. Her stormy postoperative course complicated especially by pulmonary thrombosis and infarction and by wound separation and infection is typical of patients with sickle cell anemia.

It was unfortunate that the breast lesion was not discovered until late in the pregnancy. The patient said the mass had been present for at least nine years, but that growth did not take place until six weeks before mastectomy. It seems likely that the original lesion was benign, probably a fibroadenoma, and that it underwent malignant degeneration as a result of the pregnancy.

This case further illustrates the hazards of radical mastectomy in advanced pregnancy, even without the added complication of sickle cell anemia. The pulmonary hypoventilation of late pregnancy increases the difficulties of anesthesia and is a factor in producing pulmonary complications.

Summary

1. A case of sickle cell anemia and carcinoma of the breast complicating pregnancy in a 28 year old Negress is presented.

2. A macerated fetus was born four days after radical mastectomy.

3. Death of the patient occurred nine and one-half months after mastectomy from metastases to the liver and skeleton. Sickle cell anemia was considered a factor in her death.

4. The unfavorable effects of pregnancy on both sickle cell anemia and carcinoma of the breast are discussed.

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BRAIN ABSCESS AND MENINGITIS ASSOCIATED WITH A PLEUROPNEUMONIA-LIKE ORGANISM: CLINICAL AND BACTERIOLOGICAL OBSERVATIONS IN A CASE WITH RECOVERY *

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The rôle of the pleuropneumonia group of microörganisms as human pathogens is still far from clear. In the case reported here a pleuropneumonia-like organism was repeatedly cultured from the central nervous system of a patient with a brain abscess and meningitis. This case is of interest because it probably represents the first one in which a pleuropneumonia-like organism was recognized in association with an infection of the central nervous system. The characteristics of the organism were studied in some detail.

Literature

The literature concerning the pleuropneumonia group of organisms was reviewed in 1941 by Sabin.[1] This group of microörganisms has been conclusively implicated as natural pathogens only in animals. They produce contagious pleuropneumonia bovis,[1] contagious agalactia in sheep and goats,[1] polyarthritis in rats [2] and catarrh of the upper respiratory tract in mice.[3] Similar organisms have been isolated from a wide variety of sources including the organs and nasal secretions of the respiratory tracts of rats and guinea pigs,[4] the human genitourinary tract,[5] the brains of mice,[6, 7] embryonated hens' eggs [8] and the bovine genital tract.[9] Organisms of this group seem to be largely parasitic, though they may produce infections under experimental conditions. The organisms isolated from human and animal sources seem highly species specific. Saprophytic pleuropneumonia-like organisms have been isolated from sewage.[10]

Microörganisms are placed in the pleuropneumonia group entirely on the basis of morphological and cultural similarity to the organism producing contagious pleuropneumonia bovis. In the latest edition of Bergey's Manual [11] cultures of these organisms are described as characteristically pleomorphic, with small granules, bacilli, bacillary filaments and round forms varying in size from a few tenths of a micron to 10 micra or more. Autolyzed round forms may coalesce into large empty blebs. The smallest growing units may be no larger than 0.15 to 0.28 micron and may pass through filters that retain most bacteria. In broth cultures there may be no visible evidence of growth and the organisms may not be seen in the ordinary gram-stained smear of the broth cultures. Stained smears of the centrifuged sediment of broth cultures, however, show the small gram-negative pleomorphic organisms.[1] On solid agar, the colonies

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† Research Fellow, American College of Physicians.

are very small, ranging from 0.01 to 0.6 mm. in diameter; they are slightly elevated and have a nipple-like darker center. Surface colonies on agar can be stained only by making an impression smear of the entire colony.

The pleuropneumonia-like organisms isolated from animals and man require the presence of animal proteins in the culture medium for growth, whereas the saprophytic strains from sewage have no such growth requirement.[12] Some of these organisms are facultative and some obligate anaerobes.[13] The presence of sugars in the media seems to enhance the growth of some strains.[12]

Interest in the possibility that this group of organisms might play a part in the causation of arthritic diseases in man arose from the observations of similar lesions in cattle, sheep and rats associated with pleuropneumonia infections. A recent review by Dienes, et al.[12] summarizes the results of investigations designed to assess the rôle of these organisms in human genitourinary and joint diseases. These workers concluded that pleuropneumonia-like organisms may be a part of the normal bacterial flora in the uterine cervix and vagina of the female but their isolation in pure culture from certain inflammatory processes in the female genital tract suggests that they may at times be pathogenic. Dienes et al. found this group of organisms much less often in the normal male genitourinary tract and considered that the case for pathogenicity in the male was stronger inasmuch as all of the patients from whom pleuropneumonia-like organisms were recovered had urethritis, prostatitis or cystitis. Gonococci were present simultaneously in only two of the 58 male patients yielding pleuropneumonia-like organisms. Studies were also made of the possible relationship to Reiter's syndrome. It was interesting from this standpoint that 18 of the 58 male patients had an acute arthritis and 9 of these 18 also had urethritis and conjunctivitis. Pleuropneumonia-like organisms were recovered from the synovial fluids as well as the genitourinary tract of two of the patients with the triad of urethritis, conjunctivitis and arthritis (Reiter's syndrome) but they were not obtained from other sites in any of these patients.

An organism isolated from a case of subacute bacterial endocarditis and considered to be "pleuropneumonia-like" or a Grahamella [14, 15] would not seem to belong to this group on the basis of its characteristics.[12, 16]

Gold salts have been reported as being effective in the treatment of arthritis in mice due to a pleuropneumonia-like organism.[17] Sulfonamides [18] and penicillin [19] have little effect on these organisms. Streptomycin has been reported as being effective against rat arthritis [20] due to an organism whose properties do not definitely place it in the pleuropneumonia group.[16] The in vitro sensitivity to streptomycin of some organisms in this group has been reported as 20 μ g. per ml.[13] In seven of eight cases of genitourinary infection, pleuropneumonia-like organisms disappeared during treatment with streptomycin.[13] Improvement on streptomycin therapy occurred in six patients with arthritis or Reiter's syndrome, in whom there were positive cultures for these organisms from the genitourinary tract.[18]

Dienes et al.[13] have described the appearance of pleuropneumonia-like organisms in cultures of *Hemophilus influenzae* and *Escherichia coli* on exposure of these cultures to penicillin. Whether this represents the evolution of an altered strain of the parent organism or the appearance of a symbiont is not yet clear.

Case Report

A 20-year-old white male was admitted to the Boston City Hospital on October 5, 1946, four hours after an altercation during which the stem of a smoking pipe was thrust into his left eye and was broken off flush with the skin. At operation, shortly after admission, the pipe stem was removed and it was found that the stem had penetrated the left orbit just lateral to the inner canthus without puncturing the globe and entered the brain via the superior orbital fissure. Some of the pertinent data of this patient's illness are shown in figure 1.

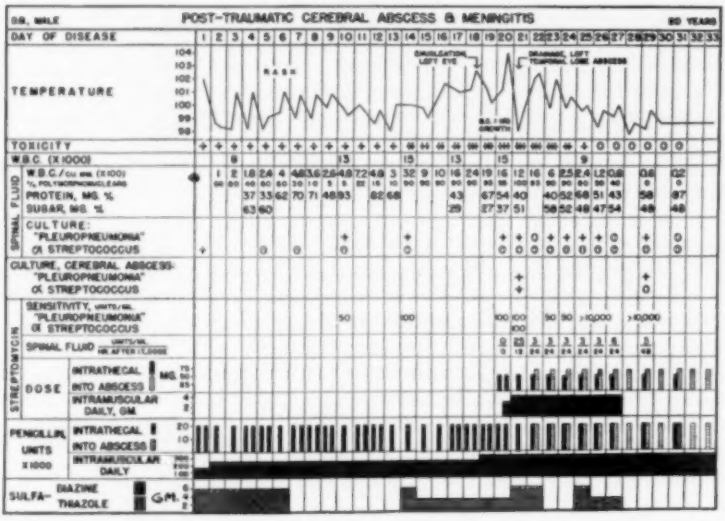

FIG. 1. **Clinical course, antibiotic and chemotherapy and significant laboratory findings.**

Sulfadiazine by mouth and penicillin, intramuscularly as well as intrathecally, were begun on the day of admission. An alpha hemolytic streptococcus was cultured from the cerebrospinal fluid on the day of admission but not thereafter. On the sixth day the sulfadiazine was discontinued because of a skin rash. The patient continued to be febrile and on the thirteenth day of illness he developed severe headache and a stiff neck. His condition became progressively worse during the next few days. The cerebrospinal fluid at this time showed an increase in polymorphonuclear leukocytes and decrease in the sugar content. Sulfathiazole was then begun by mouth and enucleation of the left eye was performed on the eighteenth day without apparent beneficial effect.

At this time, Miss Marion E. Lamb of the Bacteriological Laboratory in the Mallory Institute of Pathology reported the presence in the cerebrospinal fluid cultures of a small, slowly growing and pleomorphic gram-negative bacillus. Reëxamination of earlier cerebrospinal fluid cultures which were still being incubated showed that this organism was present as early as the tenth day of disease. A blood culture was negative for this organism.

Streptomycin was begun, intramuscularly and intraspinally on the twentieth day of illness. At this time the patient was delirious and the cerebrospinal fluid showed

a pressure of 420 mm. of water and a sugar content of 37 mg. per 100 c.c. On the following morning the patient was drowsy but rational, the temperature was lower, the cerebrospinal fluid pressure was still elevated to 460 mm. though the sugar had risen to 57 mg. At this time, an abscess in the left temporal lobe was drained through the left orbit of about 10 ml. of greenish pus, which on culture yielded an alpha hemolytic streptococcus and the small pleomorphic gram-negative bacillus. A catheter was left in the cavity (figure 2) and streptomycin solution, 5 to 10 mg. per c.c., was instilled twice daily through the catheter.

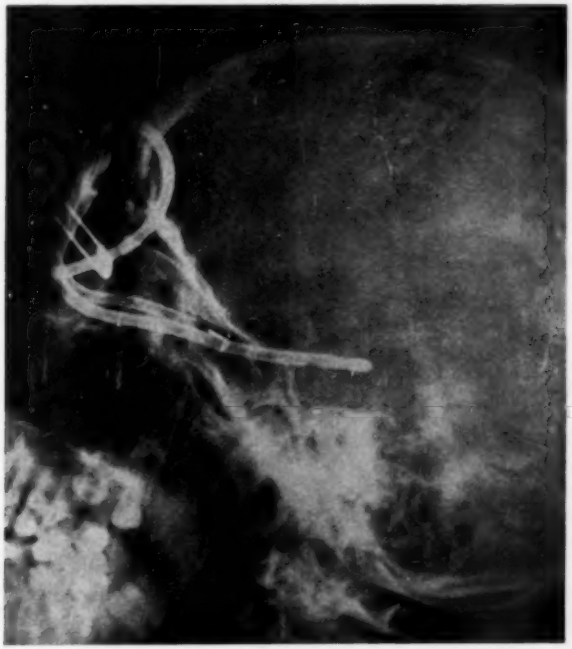

FIG. 2. Roentgenogram showing the region of the abscess in lateral view with catheter in place.

Following the surgical drainage of the brain abscess the patient improved rapidly despite the fact that cultures of the cerebrospinal fluid continued to yield the same small pleomorphic microörganism. This organism, when originally isolated was found to be moderately sensitive to the action of streptomycin being completely inhibited by 50 to 100 micrograms per ml., but after five days of treatment with the antibiotic, it was found to be highly resistant to streptomycin so that it grew uninhibited in a concentration of 10,000 micrograms per ml. This streptomycin-resistant organism was still present in cultures of the cerebrospinal fluid and in cultures of the drainage from the cerebral abscess two days after cessation of the seven-day parenteral course of streptomycin. Two days later, cultures of the cerebrospinal fluid were negative. No further drainage occurred from the cerebral abscess, the catheter was gradually withdrawn and healing took place. Some defect in recent memory per-

sisted for several weeks after recovery but there was no evidence of vestibular or cochlear dysfunction.

When the nature of this pleomorphic microörganism was suspected, questioning revealed no previous history of venereal disease, urethral discharge, dysuria, painful, swollen or stiff joints, prolonged or recent diarrhea, conjunctivitis or skin rashes. The last sexual exposure was stated to have occurred about one year prior to the present illness. Repeated cultures from the eye socket, conjunctiva, throat, urethra and prostatic secretions, immediately following recovery as well as several times during the year following discharge from the hospital failed to yield the pleomorphic organism. These cultures were made in serum enriched broth and on horse blood agar plates, both with and without penicillin incorporated in the media to suppress other flora.[19, 21, 22]

Bacteriological Studies

Isolation. The organism was initially isolated from blood-broth cultures of cerebrospinal fluid by subculturing to the surface of 10 per cent sheep blood agar plates. From most of the specimens of cerebrospinal fluid, growth was obtained by streaking the fluid directly onto the surfaces of blood agar; in some other specimens, however, growth of the organism was not obtained in this fashion but only after subculture of blood broth into which the cerebrospinal fluid had been originally inoculated.

Morphology and Cultural Characteristics. On sheep blood, horse blood or horse serum agar plates pin-point colonies appeared after two to four days' incubation at 37° C. These colonies were slightly elevated, with nipple-like centers and were 0.5 mm. or less in diameter. The colonies seemed to be fixed firmly to or embedded in the agar and could not be stained in the usual fashion by streaking a platinum loop across the colonies and then suspending the material in saline or distilled water on a slide and then fixing the smear. Impression smears of colonies, however, could be stained by the Gram or Giemsa method. Under these circumstances the stained smears showed globoid structures and amorphous masses similar to those described by other workers.[1, 13]

Visible growth could not be detected by inspection in serum broth or in horse blood broth cultures when such cultures were compared with uninoculated tubes of media incubated for the same period of time. In both types of media, whether inoculated or uninoculated, very slight clouding and a faint precipitate appeared; in the case of the blood broth, slight darkening of the button of red blood cells took place after several days of incubation. Proof of a positive broth culture was obtained only by subculturing to the surface of horse blood agar, with the subsequent appearance of the pin-point colonies, which did not occur in any of the control cultures.

The microscopic morphology of the organism was studied by means of gram-stained smears of the centrifuged sediment of serum-broth cultures. Young cultures, after one to three days' incubation, showed short or slightly elongated gram-negative bacilli and bacillary filaments. Some of the latter exhibited a darkened bead-like portion, and there were also some separate and more densely stained granular bodies. Older cultures showed an increase in the small dark granules and a decrease in the filamentous forms. After two weeks' incubation there were fewer bacillary forms, more granules, some round globoid forms

attached to bacillary filaments and some empty bleb-like structures. At all stages the organisms took the stain poorly.

Animal or human serum was necessary for growth in both the liquid and solid media. Meager growth occurred in broth containing 1 to 2 per cent horse serum; optimum growth took place in 5 to 20 per cent horse serum broth and growth did not take place in 50 or 100 per cent horse serum. The organisms did not grow on serum-enriched eosin-methylene blue agar or in serum-thioglycollate broth. Good growth occurred on egg-yolk medium and also in the yolk sacs of embryonated hens' eggs. Growth occurred best aerobically at 37° C. There was no evidence that growth occurred either anaerobically or under partial anaerobiosis such as was obtained in the candle jar. Viable organisms persisted in serum broth or blood broth cultures on incubation at 37° C., from two to five weeks and on storage in the refrigerator at 5 to 10° C. up to nine weeks. Horse serum broth cultures of this organism did not pass Seitz filters but did pass Berkefeld filters which retained a staphylococcus.

Biochemical Tests. Production of indol, ammonia or H_2S could not be demonstrated, nor was there any nitrate reduction, citrate utilization, gelatin liquefaction nor fermentation of dextrose, sucrose, lactose, xylose, levulose, maltose, mannitol, dulcitol and salicin. Reductase and catalase were not produced. The organisms were methyl red negative and Voges-Proskauer negative. No hemolysin was produced for human, horse or sheep red blood cells. Staphylococcus "V" factor did not enhance growth.

Pathogenicity for White Mice. It was impossible to produce disease in either adult or three week old white mice on injection of the organisms intraperitoneally, intracerebrally or into the foot pad. The infecting doses that were used varied from undiluted serum-broth cultures to the centrifuged sediment of up to 30 ml. of serum-broth cultures resuspended in about 1 ml. of saline.

Serologic Studies. An attempt was made to produce an antiserum in rabbits by the intravenous injection of cultures of this organism. The injections were carried out over a 12-month period and at no time was it possible to demonstrate the presence of agglutinins in the rabbits' serum. It was likewise impossible to demonstrate agglutinins in sera obtained from the patient during the acute stage of illness as well as three months after recovery. This organism did not agglutinate in rabbit serum * containing agglutinins against a pleuropneumonia-like organism originally isolated from a human genitourinary tract.[23]

Effect of Antibiotics. Strains of this organism not previously exposed to streptomycin were inhibited by 25 to 100 μg. of this antibiotic per ml. by either the tube dilution or agar streak methods of determining sensitivity. When grown on the surface of horse blood agar containing streptomycin, the organism became streptomycin resistant after the first exposure to the antibiotic. The minimum inhibiting concentration could be increased quite regularly from about 50 μg. per ml., up to 5000 μg. per ml. after such a single exposure.

Both the streptomycin sensitive and the streptomycin resistant strains isolated from the patient were resistant to the action of penicillin and grew readily in concentrations of 2500 to 5000 units per ml.

Sensitivity determinations with certain other antibiotics were carried out by the tube dilution method using one streptomycin sensitive strain of this organism.

* Prepared and provided through the courtesy of Dr. Albert B. Sabin.

The concentrations of these antibiotics required for complete inhibition were as follows: bacitracin * [24] 15.6 units per ml., polymyxin † [25] 1000 units per ml. and aureomycin hydrochloride † 0.25 μg. per ml.

Discussion

The rôle of the pleuropneumonia-like organism as a pathogen in this patient is difficult to assess. Though it was present throughout the course of the patient's illness, an alpha hemolytic streptococcus was also present initially in the cerebrospinal fluid and in material evacuated from the brain abscess. It is possible that the streptococcus in the brain abscess was responsible for the continuation of symptoms and signs which were eventually relieved by drainage of the abscess. The pleuropneumonia-like organism was still present after the abscess was drained despite the local and systemic administration of streptomycin and it became resistant to this antibiotic. Thus it is also difficult to assess the value of the streptomycin in this situation. Possibly the streptomycin exerted some favorable effect on the course of the illness before the organisms became resistant; or the change to the drug resistant state may have altered certain properties of the organisms [26] so that they were more readily overcome by the body defenses.

In view of the alleged favorable effects of simultaneous multiple chemotherapeutic and antibiotic agents it is of interest that resistance to streptomycin in this instance occurred in spite of concomitant use of sulfonamides orally and penicillin and streptomycin both intramuscularly and intrathecally.

It is of interest to speculate on the possible source of the pleuropneumonia-like organism in this case. It may have been present in the mouth of the person smoking the pipe involved in this case. Such organisms have been isolated from cultures of the respiratory tract but they may represent variant forms of other bacteria.[18] Since pleuropneumonia-like organisms have been cultured frequently from the conjunctivae of mice [1] it is conceivable that the organisms involved in this patient may have been present in the conjunctiva of the eye through which the pipe stem was passed. Thus far, however, such organisms have not been found in the conjunctiva of man.[13, 27]

The efforts in this laboratory to demonstrate agglutinins against this microorganism may have been unsuccessful because of the failure to obtain an antigen of sufficient concentration and this, in turn, was due to the poor growth of the organism. Unlike Warren and Sabin's experience [23] more vigorous growth of this bacterium could not be achieved by frequent transfers of large inocula in media containing considerable amounts of animal serum.

Conclusions

A case of meningitis and brain abscess from which an unusual organism was repeatedly cultured is reported. The patient failed to improve during treatment with sulfonamides and penicillin but recovered rapidly after the abscess was drained and streptomycin was used locally and systemically.

The organism was initially sensitive to streptomycin but became resistant to this antibiotic and persisted during the course of therapy.

* Obtained from Dr. Frank L. Meleney.
† Furnished by the Lederle Laboratories.

The growth characteristics and morphologic features of this small pleomorphic gram-negative bacillus probably place it in the pleuropneumonia group of microorganisms.

ACKNOWLEDGMENTS

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THE ELECTROCARDIOGRAM IN ALKALOSIS *

By Lewis W. Woodruff, M.D., F.A.C.P., *Joliet, Illinois*

Because of the infrequent opportunity to observe the striking, transient changes in the electrocardiogram of patients with severe alkalosis, the following case history with electrocardiograms during, and after recovery from, severe alkalosis is presented.

Case Report

The patient was a 58 year old prison guard, who was admitted to the hospital on April 13, 1947, because of profound weakness, attacks of fainting, nausea, and mental confusion.

The history began in 1937, when he first had upper abdominal pain of a colicky type, several hours after meals relieved by taking food. In 1941 he had a severe hemorrhage with markedly tarry stools, requiring hospitalization and four blood transfusions. He was relatively symptom-free until January 1946, when he had a recurrence of the same symptoms as in 1937, which, as before, were attributed to gall-bladder disease, because of a non-functioning gall-bladder by cholecystogram. In September 1946, the colicky type of pain became more burning in character with the onset of frequent vomiting spells, which resulted in the loss of 75 pounds in weight in about four months. Small amounts of bloody emesis occurred in January 1947. He then was under observation for two weeks in a Chicago clinic where a diagnosis of peptic ulcer was made. He was put on a Sippy type regime and advised that surgical treatment would probably be necessary later. Because of the acute illness of his wife, he was called home rather suddenly, and was then advised to continue on a typical Sippy program with hourly feedings alternating on the half-hour with 2 grams of calcium carbonate throughout the day, a total of about 24 or 28 grams in 24 hours. Two weeks after his discharge his burning distress recurred directly after food with frequent vomiting of small amounts of liquid, with only a small amount of blood

* Received for publication December 26, 1947.

appearing on one occasion. A week before his present admission he began to grow progressively weaker, developed more and more faintness whenever he stood up, nausea and vomiting became more frequent and severe. On the day of admission he fainted and lay on the floor unable to arise for some time.

Examination on admission showed a middle-aged male in a state of prostration markedly dehydrated, undernourished, disoriented, and very confused. Involuntary urination and defecation occurred. The temperature was 97°, orally, pulse was 80, of poor quality and the blood pressure was 80 mm. Hg systolic and 58 mm. diastolic. There was extreme dryness of the skin. The abdomen was markedly scaphoid; no masses were palpable. The deep and superficial reflexes gave no response. Chvostek's sign was not obtained.

Laboratory examination on admission showed a normal urine, except a faint trace of albumin and 4 to 6 hyaline casts. The blood non-protein nitrogen was 168

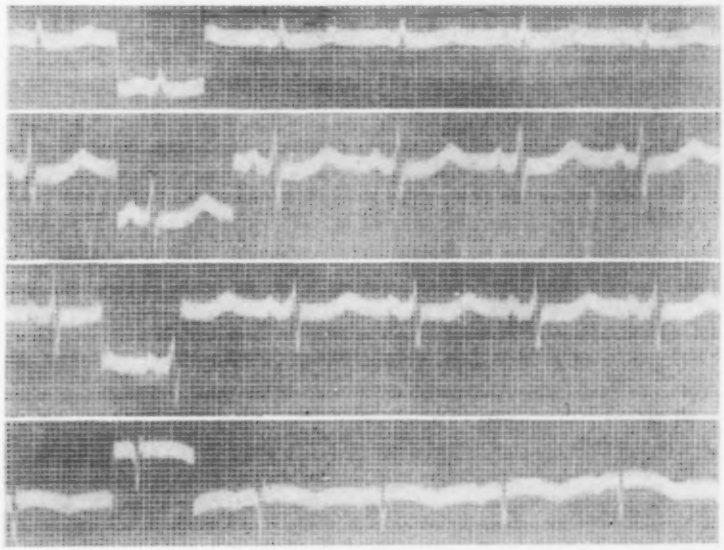

FIG. 1 A. Changes produced by alkalosis due to calcium carbonate therapy in peptic ulcer.

mg. per cent, and chlorides 300 mg. The next morning after the patient had received 2000 c.c. of normal saline by infusion, the non-protein nitrogen was 148 mg.; urea nitrogen 80 mg.; creatinine 2.8 mg.; and chlorides, 400 mg. per cent. The CO_2 combining power was 94 volumes per cent.

One week later the non-protein nitrogen was 38 mg., chlorides 600 mg. per cent and CO_2 combining power 71 volumes per cent. Gastric analysis 17 days after admission showed a maximum of free HCl of 31 and total acid of 60. The stool became negative for occult blood 12 days after admission.

Treatment consisted of infusions of normal saline with 5 per cent glucose, amino acids, vitamin B complex and ascorbic acid. Frequent small feedings of milk and cream or small bland meals with amphojel alternately were given at hourly intervals throughout the day. The patient improved rapidly, became mentally clear after the

first day. Strength gradually returned, but he continued to vomit occasionally, felt weak and faint when up and about. The blood pressure never rose above 105/68 while in the hospital. He was discharged on May 3, 1947.

Roentgen-ray examination about two weeks later showed a markedly dilated stomach with a severe pyloric obstruction.

He was readmitted on May 21 for operation, which showed a markedly dilated stomach with two large thick scars, one at the pylorus, the other a short distance distal to the pylorus. A gastric resection of approximately three-fifths of the distal portion was done with a Hoffmeister type of anastomosis. The patient made an uneventful recovery. Four months later, when last seen, he was back to normal weight and felt perfectly well.

The Electrocardiograms

The electrocardiogram on the first hospital day showed, most strikingly, a markedly prolonged QT interval of .55 second, the prolongation being entirely

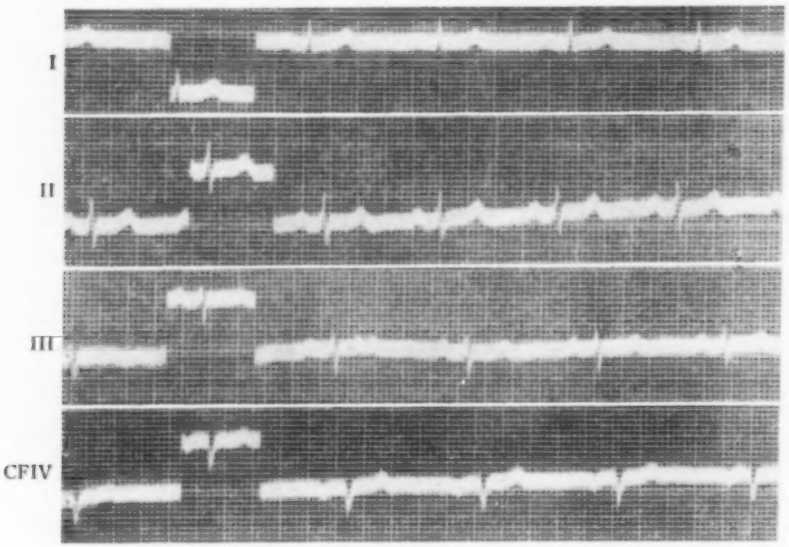

Fig. 1 B. Apparent complete return to normal after recovery.

in the latter (repolarization) period of the ventricular complex. Ventricular systole was much longer than diastole. There was also a depression of ST of about 1 mm. in the limb leads and a slight elevation in the single chest lead. The T waves in all leads were much widened, upright in the limb leads with a maximum of 3.5 mm. and inverted in the chest lead to 2 mm. There was a large QS wave of 5 mm. with no R wave. The electrocardiogram which was taken on the sixteenth hospital day was of normal appearance. The QT interval measured .38 second with a rate of 65. The QRST complexes were of normal configura-

tion though the voltage was somewhat decreased in Leads II and III. The ST intervals were all at the baseline. The QS in the chest lead was 4 mm., the R wave still absent and the T wave now upright.

Comment

A review of the literature failed to reveal so striking an illustration of the effect of alkalosis on the electrocardiogram excepting in the single instance of a case reported by Lawrence and Allott,[1] in which a very similar electrocardiographic change was shown, the QT interval being .56 second and systole much longer than diastole. Their patient, however, failed to survive so that the electrocardiogram after recovery was not obtained.

Although these transient changes are well known, there is apparently no published experimental work showing the same kinds of changes.

Summary

Electrocardiographic changes, consisting of prolongation of the latter part of ventricular systole, depression of ST in the limb leads and elevation in the chest lead with inversion of T in the chest lead occurring in a patient with severe alkalosis while on alkaline therapy for peptic ulcer with complete return to normal with recovery, is presented.

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ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS: REPORT OF THE DISEASE IN A NEGRO MALE *

By John M. Vesey, *New York, N. Y.*, and Harold G. Nelson, *Stillwater, Oklahoma*

The acute form of disseminated lupus erythematosus is relatively uncommon particularly in members of the Negro race. Cluxton and Krause [1] in a comprehensive review of this disease state, "The white race seems more susceptible to the disease. However, two of the three cases reported by Keefer and Felty were Negroes." It is to be noted, however, that both of the Negro patients reported by Keefer and Felty [2] were females. Two additional cases of this disease in colored females have been reported.[3, 4]

A review of the North American literature failed to disclose any proved cases of acute disseminated lupus erythematosus in Negro males. Our source of information was somewhat limited; however, it is evident that the occurrence of the acute form of this disease in colored patients is rare. Cummer [5] and Kirby-

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From the U. S. Naval Hospital, Dublin, Georgia.
The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

Smith [6] described three male Negro children with lupus erythematosus. King and Hamilton [7] discussed seven Negro patients with lupus but did not state whether they were male or female. None of these patients, however, was considered to have the acute disseminated form of the disease.

The following case falls into the "diffuse collagen disease" group as described by Klemperer, Pollack and Baehr.[8] The patient was in a profound toxic state and presented both clinical and pathological features as described recently by Baehr and Pollack.[9]

Case Report

History: This 23 year old, colored laborer was admitted to this hospital on July 31, 1947. The history as obtained from the family and later supplemented by the patient was incomplete. Six months prior to admission there was a gradual onset of anorexia and loss of weight. During the next five months the patient experienced fever, night sweats, recurrent blood-tinged sputum and occasional bloody urine. It was also noted that he tired easily and required a great deal of sleep. In June, five months after the onset of the present illness, the patient's family noted lesions on the bridge of his nose which subsequently spread to his cheeks. During the same period, a discrete, elevated eruption began on the trunk and extended to both arms and legs. Because of these findings, as well as increasing drowsiness and malaise, the patient was admitted to a hospital on July 18. There, the relatives were told that the patient had malaria and pneumonia. Therapy consisted of an unknown amount of penicillin and supportive measures. At the request of the relatives, the patient was transferred to this hospital on July 31, 1947.

Physical Examination: The patient was an emaciated, colored male, who was unable to respond to questioning. The temperature was 102.2° F. The pulse rate was 80 and the respiratory rate was 24. The blood pressure was 84 mm. Hg systolic and 40 diastolic. Over the nose and cheeks in a butterfly distribution was a confluent, raised, exfoliative type of lesion. On the chest, abdomen and both surfaces of arms and legs were small (3 to 4 mm.) macules and papules, many of which were excoriated. The palms and soles were pink and showed severe desquamation particularly of the terminal phalanges of the hands. In the axillary, epitrochlear and cervical regions were well defined, hard, tender, enlarged lymph nodes. Examination of the mouth showed tender, bleeding gingivae with a bluish discoloration. The tongue was dry but the papillae were normal. The chest showed no lag and was resonant to percussion, but there were occasional moist, inspiratory râles in both bases as well as broncho-vesicular breathing in the axillae. The liver and spleen could not be felt. There was no marked tenderness and peristalsis was present. The penis showed a dime-sized area of denudation on the ventral surface. There was questionable nuchal rigidity and bilateral non-sustained ankle clonus.

Laboratory Data on Admission: The red blood cell count was 2,140,000, hemoglobin 8 grams, and leukocyte count 2900 per cubic millimeter. The differential count was 69 per cent polymorphonuclears, 29 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophiles. No malarial parasites were observed in thick and thin blood smears. Examination of the urine revealed a specific gravity of 1.010 and 4 plus albumin. The urinary sediment showed many granular casts, 10 to 15 leukocytes per high dry field, and an occasional erythrocyte. The standard blood Kahn was negative.

Blood chemistry examinations revealed a carbon dioxide combining power of 23 volumes per cent, a non-protein nitrogen of 45 mg. per cent, and a blood sugar of 100 mg. per cent. The urine urobilinogen was negative in a 1:20 dilution.

The agglutination series showed a titer of 1:320 for typhoid H and a titer of 1:160 for typhoid O. The agglutinins for Proteus OXK, OX19, and *Brucella abortus* were not demonstrable. The blood culture was negative.

Spinal fluid examination revealed two lymphocytes, 55 milligrams of sugar per hundred cubic centimeters, 40 milligrams of protein per hundred cubic centimeters, and 690 milligrams of chlorides per hundred cubic centimeters. The spinal fluid Kahn and colloidal gold were both negative.

A portable roentgen examination of the chest showed bilateral increased markings without definite consolidation.

Course and Treatment: The following day, after receiving intravenous fluids including blood, the patient was dull but no longer stuporous. The temperature was 102° F., and the pulse rate was 120. There was no change in the physical findings. About 8:00 p.m. the patient became noisy and disoriented. This was followed by clonic convulsions with foaming at the mouth, loss of sphincter control and increase in temperature to 104.6° F. He was coughing blood streaked sputum and the stools were watery and contained blood clots. The convulsions were controlled by oral and rectal paraldehyde, but the pulse became irregular and rapid, and the respiratory rate was 48.

Examinations done on concentrated specimens of sputum failed to reveal acid-fast organisms. The stool specimens were negative for enteric pathogens.

From that time until death, the patient had only rare periods of lucidity. He continued to have fever, chills, involuntary bowel movements and micturition, and occasional severe convulsions. There were no localizing physical findings. Finally, on the afternoon of August 3, 1947, three days after admission, the respirations assumed Cheyne-Stokes character; the blood pressure fell; the pulse became too rapid to count and the patient died.

Blood cultures taken the day before death revealed *Pseudomonas aeruginosa* and another blood specimen just prior to death grew *Staphylococcus aureus,* non-hemolytic.

Autopsy Findings: Anatomical Diagnosis: Disseminated lupus erythematosus, minimal generalized lymphadenopathy, generalized desquamating erythematous skin rash with a "butterfly lesion" on the face, minimal ascites, slight fibrous pleuritis, and hydropericardium.

Gross Examination: At postmortem examination done 18 hours after death, the body was that of a well-developed, poorly nourished, colored male measuring 70 inches in length. The body was covered with a brownish erythematous rash which showed some desquamation. This rash extended over the lateral surfaces of the nose and onto the cheeks. The lymph nodes in the cervical, axillary and inguinal regions were enlarged. These varied in size from one to three centimeters in diameter. The lips were dry and scaly. The finger tips showed numerous small areas of ecchymosis. The under surface of the penis and the anterior surface of the scrotum presented a superficial area of inflammation about two centimeters in diameter.

Serous Cavities: There were approximately 500 c.c. of clear straw colored fluid with a specific gravity of 1.016 present in the abdominal cavity. The total protein content of the fluid was 3.18 gm. per cent. The pleural cavities were opened under water but no pressure changes were noted. Both pleural and pericardial cavities contained approximately 100 c.c. of straw colored fluid. The specific gravity of the fluid was 1.020. The total protein content was 4.90 gm. per cent.

Heart: The heart weighed 282 gm. and was not dilated. The surface was smooth but there were a few small dark red petechiae on the epicardium of the left ventricle. The valves were normal and no gross endocardial or myocardial changes were seen. The aorta showed a few atheromatous plaques about 6 mm. above the aortic valve. The coronary arteries were patent.

Lungs: The anterior surface of the left lung showed a few thread-like adhesions. The pleurae of both lungs showed a few scattered petechiae. The left lung weighed 685 gm.; the right lung weighed 764 gm. The dependent portions of both lungs showed hypostatic congestion. A foamy, whitish fluid was present in the trachea and bronchi. The pulmonary vessels were patent. No gross areas of consolidation were evident.

Spleen: The spleen weighed 235 gm. There were no adhesions noted. On section the pulp was not easily scraped. The splenic pulp was dark red in color.

Liver: The liver weighed 1769 gm. On section the organ was pale yellow in color. The gall-bladder contained about 25 c.c. of greenish-brown bile. The biliary ducts were patent.

Pancreas: The pancreas was not unusual and weighed 113 gm.

Adrenals: The adrenals were of average size and configuration. They showed no unusual features.

Kidneys: The left kidney weighed 247 gm. and the right 210 gm. The capsules stripped with ease leaving a smooth surface. Both kidneys were swollen and dark red in color. On section the demarcation of the cortex and medulla was not prominent.

Ureters and Bladder: The ureters were distended with urine and measured 8 mm. in outside diameter. The bladder contained about 50 c.c. of cloudy straw colored urine.

Brain and Coverings: The brain weighed 1473 gm. There were no unusual gross changes. The ventricular fluid was clear. The cerebral vessels showed no gross changes.

Microscopic Autopsy Findings *

"*Heart:* Multiple sections of heart show the architecture to be generally well preserved. Scattered throughout the myocardium are numerous foci of necrosis of the interstitial collagenous tissue. These foci of necrosis vary in size and are made up principally of chromatin dust, bits of nuclear debris, as well as the actual necrotic collagenous tissue. Small nests of plasma cells and lymphocytes are present, and occasionally some polymorphonuclear infiltration is seen. The majority, but not all, of these foci are in the vicinity of blood vessels. In other areas, foci of fibrinoid degeneration of the collagenous tissue are observed. The interstitial tissue is edematous and occasional chronic inflammatory cells are scattered throughout the interstitial tissue. The majority of the arterioles appear essentially normal but occasional ones showing swelling of the endothelium with an increase in the amount of subendothelial connective tissue. Occasional ones are surrounded by a tuft of acute and chronic inflammatory cells. The larger branches of the vascular system present in the epicardium show rather extensive changes. Many of the endothelial cells are swollen and vacuolated, and in areas have almost a cuboidal appearance. The subendothelial connective tissue shows extensive fibrinoid degeneration with actual areas of necrosis. The media is unremarkable, but the serosa is infiltrated with plasma cells, lymphocytes, and some mononuclear cells. Wandering macrophages are conspicuous about the blood vessels and particularly in the previously described areas of myocardial necrosis. The epicardium is diffusely infiltrated with chronic inflammatory cells and macrophages. In still other areas throughout the myocardium and epicardium are numerous foci of blue-staining bacteria. These bacteria are cocci, and in many instances there is an acute inflammatory response about them, almost to the point of abscess formation in some areas. In other areas, however, there is absolutely no inflammatory response to the bacteria. Such foci, however, differ considerably from the previously described foci of necrosis, particularly in regard to the

* The microscopic report was prepared by J. R. Carter, LTJG, MC, USNR, Chief Pathologist, U. S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland.

type of cellular infiltration. The majority of those foci of bacteria in which no inflammatory response is visible contain organisms which are rod shaped and presumably of the coliform group. In some areas the capillaries and vessels are intensely congested and somewhat dilated. Occasionally small foci of hemorrhage are noted in the myocardium and epicardium. In many areas the endothelial cells are swollen, vesicular and in areas assume a cuboidal appearance. The subendothelial connective tissues show extensive fibrinoid degeneration with actual areas of necrosis and inflammatory response, characterized principally, however, by plasma cells and lymphocytes. No definite vegetations are noted, but the degenerative change extends over large areas of the endocardial surface. The large coronary arteries show moderate arteriosclerotic change but are otherwise not involved by any inflammatory process. The degenerative character of the endothelial lining shows extension of the degenerative and necrotic process ramifying throughout the superficial layers of the myocardium adjacent to the subendocardial connective tissues. In such areas there is frequently an associated acute and chronic inflammatory cell response.

"*Lungs:* Sections of lungs show the architecture to be generally well preserved. There is marked congestion and dilatation of the vessels in all areas, including the pleura as well as the parenchyma. The alveolar walls are somewhat distended with red blood cells. Scattered throughout are foci of pneumonic consolidation in which the alveolar spaces are filled with red cells, leukocytes and fibrin. In other areas the alveolar spaces contain edema fluid and red cells only. Occasional small foci of interstitial hemorrhage are observed. Many of the bronchi contain large numbers of acute inflammatory cells and in areas the bronchial mucosa is hyperplastic. Myriads of dust-filled macrophages are scattered throughout. The vessels, however, appear everywhere intact and there is no evidence of an inflammatory response. Occasional nests of bacteria are present in the areas showing bronchopneumonia.

"*Spleen:* All sections show extensive and marked congestion of the sinusoids and pulp. Large areas of extravasated blood are present. The trabecular markings are more pronounced than normal and in some areas there is slight increase in interstitial fibrous tissue. The central arteries show intimal thickening and the endothelial lining is swollen in some areas. By far the most conspicuous feature, however, is the hyalinized collagenous tissue about the central arteries, so extensive in areas as to almost completely obliterate the Malpighian bodies. This hyalinized fibrous tissue is forming masses in which an onion skin or onion peel effect is noted. Where these hyalinized masses are most marked, the central vessels appear more tortuous and in some instances appear to be almost completely obliterated. The Malpighian bodies are not hyperplastic, nor is any necrotizing lesion of the central arterioles noted. There are, however, many arterioles and Malpighian bodies which do not show this peculiar hyalin mass of fibrous tissue.

"*Liver:* Multiple sections show the architecture to be well preserved. The sinusoids are slightly dilated in some areas, but the liver cords are essentially unremarkable. There are collections of chronic inflammatory cells in the portal areas, particularly about the bile ducts. No definite vascular lesions are observed, nor is there any evidence of infection or neoplasm.

"*Pancreas:* Sections show the architecture to be generally well preserved. Scattered throughout most of the sections are areas of interstitial fibrosis. In some areas this fibrosis is rather marked and in addition there is infiltration with chronic inflammatory cells, particularly about some of the blood vessels. The vascular system, however, is essentially unremarkable.

"*Adrenals:* Sections show the architecture to be well preserved. The cortical and medullary tissue appears essentially normal. No vascular lesions are observed. In some sections, however, there are rather large areas of extravasated blood in the capsule and in the areolar tissue about the adrenals.

"*Kidney:* Multiple sections show the architecture to be generally well preserved. The glomeruli are of normal shape and configuration but many of them show hyalinized thickening of the endothelial lining. In some areas this is highly suggestive of the so-called 'wire loop' capillaries. The endothelial cells in areas are swollen and occasional polymorphonuclear leukocytes are present in the glomeruli. Bowman's capsules in some regions show increased hyalinization. There are focal areas of degeneration of the tubular epithelium with other areas showing evidence of regeneration. Scattered throughout the parenchyma, more particularly in the cortex, are numerous foci of necrosis, about which a few acute and chronic inflammatory cells are seen. In still other areas deposits of bacteria are conspicuous, and about these bacteria are large numbers of acute and chronic inflammatory cells to the extent of abscess formation. Large amounts of calcareous material are present in the tubules, many of which contain albumin and hyalin casts. Other tubules contain large numbers of red blood cells. Some of the tubules are dilated and moderately tortuous, while others appear atrophic. The arteries and arterioles show no pronounced changes; a few show hyalinization of their walls and the majority are congested and moderately dilated.

"*Gastrointestinal Tract:* Multiple sections show essentially normal gut tissue. There are moderate autolytic changes. No definite vascular lesions are observed.

"*Lymph Nodes:* Sections show rather extensive necrosis of lymphoid tissue. These areas consist principally of necrotic debris, pyknotic nuclei, and chromatin dust. About some of these areas there is a moderate infiltration with acute inflammatory cells and in some areas there is reticulo-histiocytic hyperplasia. Some of the vessels are markedly congested, and a few of the arterioles show fibrinoid degeneration of their walls. Occasional masses of bacteria are present, but about these there is little if any cellular reaction.

"*Skeletal Muscle:* The skeletal musculature appears essentially normal. In the interstitial tissue, however, there are small foci of collagenous degeneration and necrosis with minimal infiltration with chronic inflammatory cells. Some of the vessels in the vicinity of the necrosis show marked swelling of the endothelial lining with almost complete obliteration of the lumen.

"*Brain:* Multiple sections show extensive neuronophagia as well as chromatolysis. Many of the blood vessels are congested but there is no evidence of infection, degeneration or infarction.

"*Skin:* Sections of skin show the epidermis to be generally intact. In some areas, however, there is definite ulceration with necrosis of the collagenous tissue of the dermis. The blood vessels in the areas of necrosis are thrombosed and in many instances the vessel walls show extensive fibroid degeneration and actual necrosis. The thrombi have not undergone organization. The squamous epithelium, where present, shows dyskeratosis. There is moderate parakeratosis of the surface and in many areas the prickle cell layer shows spongiosis. In still other layers the polarity of the basal cells is absent and the nuclei are rather bizarre. The basement membrane is absent in some areas but there is no definite evidence of invasion. In the ulcerated areas small clumps of bacteria are present. In one area a small epithelial inclusion cyst is noted. The vessels deeper in the dermis show endothelial proliferation, while in other areas there is degeneration of the walls. About many of these vessels there is a thin rim of chronic inflammatory cells.

"*Summary of Microscopic Findings:* The histologic appearance of the various organs studied is compatible with disseminated lupus erythematosus. The diffuse areas of necrosis of collagenous tissues, the diffuse lesions both degenerative and necrotic of the vessels throughout the body, the presence of the characteristic onion-skin hyalin masses in the spleen, the tendency for wire-loop formation in the kidneys, are highly suggestive and compatible with disseminated lupus. The clumps of

bacteria observed in many of the viscera may be ascribed to two sources: (1) *Staphylococcus aureus* septicemia was present prior to death, which incidentally is not an uncommon mode of exitus in cases of disseminated lupus. Undoubtedly some of the abscesses are on the basis of this staphylococcus septicemia. On the other hand, rod shaped organisms without any evidence of cellular response, as well as certain coccal forms again without any cellular response, suggest that the organisms were contaminants at the time of autopsy. Despite the complications by this bacterial infection, it is felt that the other lesions previously described are not related to this bacterial infection, but represent a diffuse disease of the collagenous tissues. Bronchopneumonia was present probably as a terminal event."

Comment

The clinical features together with the gross and microscopic postmortem findings in this case were suggestive of acute disseminated lupus erythematosus. Because of the rarity of this disease in members of the Negro race, we enlisted the aid of three disinterested pathologists who concurred in the diagnosis, thus encouraging us to publish this protocol.

Summary

A case of acute disseminated lupus erythematosus in a Negro male is reported.

Note: We are indebted to Dr. Orville T. Bailey, Neuropathologist and Vice-Chairman of the Neurological Institute of the Children's Medical Center, Boston, Massachusetts and to Dr. S. H. Colvin, Jr., Director of the Department of Pathology, Touro Infirmary, New Orleans, Louisiana for reviewing the clinical history and microscopic sections. Both pathologists agreed that the diagnosis was compatible with acute disseminated lupus erythematosus.

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EDITORIAL

EXPERIMENTAL DIABETES

COMPLETE extirpation of the dog pancreas by Minkowski and von Mering [1] in 1889 may be viewed as the first approach to the production of experimental diabetes. It was this fundamental experiment which led, 33 years later, to the isolation of insulin by Banting and Best.[2] Since 1922 further elucidation of the complexities of carbohydrate metabolism has been achieved by physiological experimentation. Numerous studies have led to the knowledge that the metabolic activity of these foodstuffs is not solely under the control of the beta cell hormone of the pancreas, but involves regulatory activities of other endocrine glands. Continuing apace with these physiological investigations have been biochemical studies which have resulted in clarification of many of the steps involved in the intermediary metabolism of carbohydrate. The work of Cori [3] and others in recent years has produced significant information linking even closer these two lines of investigation. Advances have also been made possible by the recent employment of new tools for the production of experimental diabetes. There is reason to believe that the etiological mysteries which still shroud the origin of human diabetes mellitus may be partly clarified in the not too distant future.

In 1930, Houssay and Biasotti [4] demonstrated that the experimental diabetes produced by total pancreatectomy could be ameliorated by hypophysectomy. The subsequent injection of anterior pituitary extracts resulted in the return, in full force, of the diabetic condition. Thus was demonstrated for the first time the antagonistic relationship of the hypophysis and pancreas in the regulation of carbohydrate metabolism. This concept was strengthened by later studies [5] which revealed that the prolonged injection of anterior pituitary extracts into intact or only partially pancreatectomized animals, could also result in either temporary or permanent diabetes. The latter studies, furthermore, permitted direct histological examination of the islets of Langerhans. It was revealed that under APE stimulation the beta cells underwent degranulation, hydropic degeneration and eventually decrease in number. Young [6] called attention to the existence of a tempo-

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[2] Banting, F. G., and Best, C. H.: The internal secretion of the pancreas, Am. J. Physiol. **59**: 479, 1922.

[3] Cori, C. F.: The Harvey Lectures, 1945–1946, Vol. 41, p. 253, Science Press Printing Co., Lancaster, Pa.

[4] Houssay, B. A., and Biasotti, A.: Hypophysectomie et diabete pancreatique chez le crapaud, Compt. rend. Soc. de biol. **104**: 407, 1930.

[5] Houssay, B. A., Biasotti, A., and Rietti, C. T.: Diabetogenic action of anterior lobe extracts, Compt. rend. Soc. de biol. **111**: 479, 1932.

[6] Young, F. G.: Metabolism in experimental diabetes mellitus, Lancet **2**: 955, 1948.

rary (idiohypophyseal) diabetes which disappeared when APE injections were stopped and a permanent (metahypophyseal) diabetes which persisted after prolonged injections of potent extracts. The latter variety was characterized by the degenerative beta cell changes mentioned above. Metahypophyseal diabetes is, in essence, true pancreatic diabetes. In the course of these studies various discordant facts have been noted which are still unexplained. For example, there are species and age differences in the response to APE injection. Furthermore, Young has observed spontaneous amelioration of the metahypophyseal diabetes in several of his experimental animals. No explanation could be afforded.

Young's studies have indicated a close relationship between the diabetogenic activity of his extracts and the growth hormone of the anterior pituitary. It is interesting in this connection to point out the significantly elevated incidence of diabetes mellitus among patients with acromegaly.[7] Other investigators have observed a close relationship between diabetogenic activity and the adrenocorticotropic hormone (ACTH) of the anterior pituitary.[8] The use of purified preparations of ACTH recently in the experimental animal as well as in the normal human subject has verified the diabetogenic potentialities of ACTH.[9] The implication of the adrenals in the regulation of carbohydrate metabolism had been foreshadowed by the experiments of Houssay and his collaborators.[10] These investigators found that removal of the adrenals in pancreatectomized animals had an ameliorating effect upon the diabetes similar to that following hypophysectomy. The administration of some adrenal cortical steroids has been observed to produce hyperglycemia and glycosuria in the experimental animal.[11] The disturbance in carbohydrate metabolism was of a temporary nature and disappeared with cessation of the injections. Other endocrines have likewise been implicated experimentally, and to a certain extent clinically, in the overall regulation of carbohydrate metabolism.[12] Space limitations forbid an extended discussion of these additional factors.

There are, of course, many important implications of the studies cited above. First and foremost, perhaps, is the concept that diabetes mellitus may not only arise from an absolute deficiency of insulin (pancreatectomy), but may occur, either on a temporary or permanent basis, due to a relative insulin deficiency induced by the over activity of antagonistic hormones. The

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latter variety is of particular clinical interest since histological studies in the experimental animal indicate that islet cell degeneration results from "exhaustion" due to overwork. This concept has recently received support from the experimental studies of Dohan and Lukens [13] who produced a permanent type of diabetes in cats by the repeated injection of massive amounts of glucose. Histological study of the pancreas in their animals revealed degenerative changes in the beta cells similar to those seen in pituitary—induced diabetes. It should be emphasized, however, that in the study of clinical diabetes mellitus only rare instances of gross endocrine antagonisms, such as those produced experimentally, are encountered. In the vast majority of human cases of diabetes mellitus the pathogenetic mechanisms are quite obscure. Nevertheless, the concepts provided by experimental study are of fundamental importance.

The endocrine antagonisms demonstrated by physiological experimentation have recently been partially clarified by important biochemical investigations. To all intents and purposes glucose is metabolically inert until it undergoes phosphorylation to glucose-6-phosphate.[14] This key reaction is catalyzed by an enzyme, hexokinase, which is present in almost every living cell. The source of phosphate for this reaction is adenosine triphosphate (ATP). The reaction may be illustrated as follows—

$$\text{Glucose} + \text{Adenosine Triphosphate} \xrightarrow{\text{hexokinase}} \text{Glucose-6-phosphate} + \text{Adenosine Diphosphate}$$

It is from glucose-6-phosphate that the further metabolism of glucose (glycogen formation, oxidation, etc.) proceeds. Cori et al.[15] have demonstrated that the anterior pituitary produces a specific inhibitor of hexokinase. Anterior pituitary extracts when present in excess retard the phosphorylation of glucose to glucose-6-phosphate. Insulin, which has no direct action on hexokinase, abolishes the pituitary inhibition and thus permits the reaction to proceed at a rapid rate. These antagonistic relationships have been demonstrated in vitro using an isolated hexokinase system of muscle. Certain adrenocortical preparations act by prolonging the pituitary inhibition of hexokinase without exerting any direct effect on hexokinase itself. These experiments have for the first time provided actual evidence for the mode of action of insulin. Recent studies indicate also that insulin may exert an influence upon other steps in intermediary carbohydrate metabolism. Stetten [14] believes that hexokinase inhibition resulting either from relative or absolute deficiency of insulin explains most of the metabolic defects in diabetes mellitus. Inhibition of glucose phosphorylation leads to an increase in the concentration of blood glucose which soon exceeds the renal threshold

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and results in glycosuria. In order to maintain normal metabolism, with glucose not readily available, other body constituents are called upon. Reserves of glycogen are depleted, ketone body production increases and a negative nitrogen balance occurs.

Another tool has recently become available for the production of experimental diabetes. This is alloxan, an oxidation product of uric acid (figure 1). Dunn et al.[16] attempted to utilize this agent in a study designed to explain the pathogenesis of the crush syndrome. The injection of alloxan into

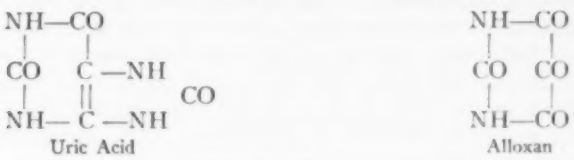

FIG. 1.

rabbits resulted in the death of their animals. Histological study revealed necrosis of the beta cells of the islets of Langerhans. By the use of smaller doses it became possible to produce permanent diabetes in surviving animals. The diabetogenic action of alloxan has since been noted in many animal species.[17] The specificity of alloxan is quite striking, for if its chemical structure is appreciably changed its diabetogenic action is lost. Injected intravenously, alloxan disappears from the blood or is destroyed within five minutes. Following its injection, there occurs a sharp drop in the blood concentration of glutathione, a sulfhydryl compound occurring widely throughout the body. This finding suggested the possibility that glutathione acted as a protective agent for the body against alloxan. In 1946, Lazarow[18] demonstrated that the diabetogenic action of alloxan could be nullified by the previous injection of glutathione. Other sulfhydryl compounds such as British Anti-Lewisite (BAL) likewise were found to exert a protective action if administered *just before* the injection of alloxan.

The administration of alloxan virtually produces a medical pancreatectomy. Its effect is not mediated through the pituitary. Treated animals are permanently and truly diabetic. Study of the alloxan diabetic animal has shed some light upon the possible function of the alpha cells of the islets. When dogs made diabetic with alloxan are subsequently pancreatectomized their insulin requirement decreased markedly.[19] Similar effects have been observed in diabetic humans who have been pancreatectomized.[20] It has

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been suggested that the alpha cells secrete a glycogenolytic hormone, i.e., one having a directly antithetical effect to insulin. Several recent studies upon the hypothetical alpha cell hormone have been reported.[21, 22] Its exact significance for normal carbohydrate metabolism is, at present, unknown.

The significance of alloxan in the pathogenesis of human diabetes mellitus is also quite unknown at this time. Alloxan has definitely been shown, under experimental conditions, to destroy human islet cells. No certain knowledge exists yet as to its mode of action. Lazarow [23] has recently exhaustively reviewed this aspect of the subject and has suggested, on theoretical grounds, that normal beta cell metabolism may render these cells peculiarly susceptible to the action of alloxan. This idea is based upon the concept that the normal synthesis of insulin may deplete the beta cell of glutathione. Although no direct evidence exists, it has been suggested that alloxan may be a normal intermediate in the metabolism of pyrimidines. Any metabolic situation calling for increased insulin synthesis and output could, by further depleting beta cell glutathione, render the latter susceptible to the action of a "toxic" agent such as alloxan. These considerations are, as yet, largely theoretical. However, several recent reports are quite pertinent in this regard.

Griffiths [24] reduced the blood glutathione level of rabbits by feeding them a methionine and cystine deficient diet. The subsequent intraperitoneal injection of uric acid produced a persistent hyperglycemia which could be reversed if the animals were placed upon a normal laboratory diet. The importance of these observations lies in the following facts: (1) blood glutathione levels can be influenced by specifically deficient diets; (2) uric acid, a normal metabolite closely related to alloxan, can produce transient diabetes. A more pertinent study is that of Conn et al.[25] The administration of ACTH to normal humans has been observed to produce a metabolic state resembling clinical diabetes mellitus. Associated with the hyperglycemia, glycosuria, etc., these workers have observed a fall in blood glutathione level. In one subject glutathione was administered concomitantly with ACTH and produced a sharp drop in blood glucose level as well as diminished glycosuria. This effect was transitory lasting only for several hours after the administration of glutathione.

Many of the very recent studies in experimental diabetes have provided ideas which are in need of further substantiation. Nevertheless, the greater clarity of knowledge achieved thus far holds forth promise that these studies will advance our understanding of etiological mechanisms in human diabetes mellitus.

MILTON S. SACKS

[21] Sutherland, E. W., and Cori, C. F.: Influence of insulin preparations on glycogenolysis in liver slices, J. Biol. Chem. **172**: 737, 1948.

[22] Heard, R. H. D., Lozinski, E., Stewart, L., and Stewart, R. D.: The alpha cell hormone of the islets of Langerhans, J. Biol. Chem. **172**: 857, 1948.

[23] Lazarow, A.: Factors controlling the development and progress of diabetes, Physiol. Rev. **29**: 48, 1949.

[24] Griffiths, M.: Uric acid diabetes, J. Biol. Chem. **172**: 853, 1948.

[25] Conn, J. W., Louis, L. H., and Johnston, M. W.: Alleviation of experimental diabetes in man by administration of reduced glutathione (GSH); metabolic implications, Science **109**: 279, 1949.

REVIEWS

Selective Partial Ablation of the Frontal Cortex: A Correlative Study of Its Effects on Human Psychotic Subjects. By the Columbia Greystone Associates, FRED A. METTLER, M.D., Ph.D., Editor. 517 pages; 18 × 26 cm. Paul B. Hoeber, Inc., New York. 1949. Price, $10.00.

This volume is a chronicle of the most carefully planned, most critical and best-controlled study of the effects of frontal-lobe ablation on institutionalized psychotic patients that has been attempted since lobotomy was introduced in 1936. In fact, it is the design of the clinical experimental method reported here which impresses one, rather than the information which resulted from the study. There is little new which emerges regarding the form and function of the human frontal lobe or the structure of any psychotic process.

Two groups of 24 psychotic patients, matched as nearly as possible in sex, age and type of illness, were studied and treated alike until the time of operation. At that point the control group was anesthetized and blood was withdrawn, while in the operated group 20 different combinations of architectonic frontal-area ablations were performed. In spite of the careful attempts to select comparable groups, there was a lack of uniformity in their selective matchings and the complications ensuing therefrom interfered in some ways with the follow-up studies.

The major weaknesses of the work may be enumerated as follows: (1) failure to complete investigations before making the report, (2) meagerness of the preoperative psychiatric formulations and (3) short psychosocial follow-up of paroled patients.

Apparently, resection of the frontal area leads to few consistent modifications in the various medical, physiologic and biochemical formulations which were investigated. Resection of Brodmann's areas 9, 10, 24, 44, 45 and 47, alone or in combination, is considered to produce modifications in the glucose tolerance test, and it is stated that the frontal lobe granular cortex does exert an influence on sugar metabolism. In the early postoperative period a tendency toward elevation of the value for reticulocytes was noted. It is also stated that electro-encephalographic study of these patients supports the view that the human cortex is not essential for the development of the alpha rhythm.

One is impressed by the fact that the elaborate psychologic studies failed to disclose consistent emotional or behavioral changes as a result of the operative procedures. This confirms the opinion that psychotic patients are not good persons to use in examining the function of specific brain areas because their distorted thinking introduces a variable which cannot be controlled in either the preoperative or postoperative state. Over and above this, also, one gets the distinct impression that present-day psychologic technics are not sufficiently developed or sensitive to be used to test the limits of personality functions, particularly those subtleties of reaction which are apparent to families, friends and social workers when the patients return to society. The conclusion to be drawn, therefore, is that there is a need to develop additional psychologic methods sensitive enough to detect those nuances which render precarious the individual's ability to adjust to society.

The psychiatric studies reported upon are of a conventional variety. More information might have been obtained if a better formulation of the preoperative assets and deficits of each patient, including his predominant personality traits had been determined. While a short follow-up study can hardly be expected to provide a meaningful evaluation of the therapeutic efficiency of topectomy, at the end of seven months 11 of the 24 patients operated on were paroled from the hospital and 10 were

gainfully employed. Two of these patients had a recurrence of their psychosis and these, with one addition, had to be returned to the institution. All but one of the patients in this group had Brodmann's areas 9 and 10 removed completely or in part, either alone or in combination with other areas. One of 11 now working had only area 46 removed. Three of the 24 in the control group were paroled and had remained out of the institution at the end of 12 months.

It is postulated that the specific effect of topectomy is to alter the affective responses so that tensions do not accumulate, and thereby regressive reparative behavior becomes unnecessary. This is also the stated indication for lobectomy. Neither procedure apparently modifies the basic psychopathologic process and both often fail of accomplishment in regard to the specific effect, for after operation patients do sometimes accumulate tension, regress and require hospitalization with full-blown psychoses. Others receive no demonstrable benefit at all.

Although this procedure of topectomy may be said to indicate more precisely the frontal brain areas most concerned with the affective life of the individual, it is most unlikely that it will be extensively employed therapeutically in its present form.

FRANCIS J. BRACELAND

Arterial Hypertension: Its Diagnosis and Treatment. 2nd Ed. By IRVINE H. PAGE, M.D., and ARTHUR C. CORCORAN, M.D. 400 pages; 14.5 × 21 cm. Year Book Publishers, Chicago. 1949. Price, $5.75.

This is a well prepared and pleasantly written treatise on hypertension and related subjects, designed to be of practical value to all who undertake the care of patients suffering from arterial hypertension. Many subjects are covered beyond the immediate framework of arterial hypertension per se; thus the clinical features and treatment of congestive heart failure, coronary artery disease, and cerebrovascular accidents are thoroughly discussed. It is pleasing to find that the authors emphasize that lowered blood pressure is not a common cause of cerebral thrombosis, as is sometimes taught.

There are several innovations since the first edition: a chapter has been added on the diagnosis and treatment of hypertension other than "essential"; another on diet therapy; and an appendix describing in detail the Addis test for estimating concentrating power and sediment count, urea clearance test, measurement of mannitol and p-aminohippurate plasma clearances and tubular secretory capacity for PAH.

Treatment seems to be particularly well dealt with, and the chapter which appraises the place of sympathectomy in hypertension is excellent.

While the authors undoubtedly place emphasis on practice rather than theory, they have by no means ignored theoretical considerations. Thus, all the practical detail that the general practitioner and internist could wish for in handling hypertensive patients is presented, but in addition there is a very adequate discussion of the important theoretical aspects of arterial hypertension.

The whole readable text combines the virtues of being both up-to-date and, at the same time, well balanced. All in all this is a book of exceptional merit.

H. J. L. M.

Borderlands of Psychiatry. 5th Ed. (Harvard University Monograph in Medicine and Public Health—No. 4.) By STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. 166 pages; 16 × 23.5 cm. Harvard University Press, Cambridge, Mass. 1943. Price, $2.50.

This is a volume which constitutes a series of essays on subjects falling within the twilight zone of medicine, neurology, and psychiatry. An ardent and urgent plea is voiced for the study and research in the fields of speech defect, epilepsy, the psycho-

neuroses and other emotional maladjustments. The significance of this plea is most apparent when one recalls that six and a half million of our population fall into the enumerated groups. Where indicated, basic physiologic tenets are reviewed for adequate understanding. This is a stimulating volume for those whose activities encompass the "borderlands" of psychiatry, but is not intended for purposes of primary reference.

H. W. N.

Bentley's Textbook of Pharmaceutics. 5th Ed. Revised by HAROLD DAVIS, B.Sc., Ph.D. (Lond.), Ph.C., F.R.I.C., Pereira Medallist, Sometime Chief Pharmacist, University College Hospital, London, with the collaboration of M. W. PARTRIDGE, B.Pharm., B.Sc., Ph.D. (Lond.), Ph.C., Lecturer in Chemistry, University of Nottingham, and A. I. ROBINSON, Ph.C., Late Pharmacist in Charge, Manufacturing Laboratory, Messrs. Stafford Allen & Sons, Ltd., London, with contributions by W. A. BROOM, B.Sc. (Lond.), F.R.I.C., M. ELLIS, M.Sc. (Wales), F.L.S., and H. A. TURNER, B.Sc. (Lond.), Ph.C., D.B.A (Pharm. Soc.), Pereira Medallist. 1100 pages; 14.5 × 22.5 cm. The Williams and Wilkins Co., Baltimore, Md. 1949. Price, $7.50.

This book presents the principles and fundamentals employed in the practice of pharmacy. After including a short history of the British Pharmacopoeia in Part 1, Part 2 discusses the processes and small scale apparatus employed in the formulation and perfection of pharmaceutical products on a retail or small hospital level, explaining many of the principles on a physical and physical chemical basis. Part 3 deals with the large scale manufacturing of pharmaceutical products, including the handling of raw materials, heat and power requirements, materials of construction, the Factories Act and safety, and a discussion of the unit processes and the equipment employed in the large scale manufacture of pharmaceutical products, with a brief explanation of mechanical and engineering problems. Part 4 discusses the usual principles involved in the preparation and dispensing of pharmaceutical products. Part 5 includes the subject of bacteriology, antibiotics, disinfection, sterilization, and the preparation of parenteral preparations, vaccines and sera. Part 6 discusses surgical dressings, sutures and ligatures. Part 7 consists of a systematic study of the preparations of the 1948 British Pharmacopoeia and makes some reference to the more important preparations, etc., in the British Pharmacopoeial Codex, and the United States Pharmacopoeia, and to some of the more widely used non-official products. The appendix includes a table of doses of the more important medical products of Great Britain, but fails to give any recommendations for penicillin and does not mention streptomycin, aureomycin and some of the newer antibiotics.

This book includes a number of topics that are not included in most of the pharmaceutical textbooks and reference books used in this country. For this reason, it should be of special value to pharmaceutical libraries, teachers of pharmacy, and practicing pharmacists who wish to keep informed on pharmaceutical progress in the British Empire. It will occasionally serve the internist as a reference volume.

N. E. F.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Surgery. Volume II. Editorial Board: WILLIAM DEWITT ANDRUS, New York, Chairman; HUGH CAIRNS, Oxford; EDWARD D. CHURCHILL, Boston; CLARENCE CRAFOORD, Stockholm; LESTER R. DRAGSTEDT, Chicago; EMILE HOLMAN, San Francisco; JOHN S. LOCKWOOD, New York; D. W. GORDON MURRAY, Toronto; ALTON OCHSNER, New Orleans; and ISIDOR S. RAVDIN, Philadelphia.

590 pages; 23.5 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, $11.00.

Clinical Pathology: Application and Interpretation. By BENJAMIN B. WELLS, M.D., Ph.D., Professor of Medicine, University of Arkansas School of Medicine. 397 pages; 24 × 15.5 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $6.00.

Congenital Anomalies of the Heart and Great Vessels: Clinicopathologic Study of 132 Cases. By THOMAS J. DRY, ROBERT L. PARKER, H. MILTON ROGERS, JESSE E. EDWARDS, HOWARD B. BURCHELL, and ARTHUR H. BULBULIAN, of The Mayo Clinic. 68 pages; 27.5 × 20 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $4.50.

Electrocardiography: Fundamentals and Clinical Application. By LOUIS WOLFF, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital, etc. 187 pages; 25 × 16.5 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $4.50.

Essential Urology. By FLETCHER H. COLBY, M.D., Chief of the Urological Service, Massachusetts General Hospital, etc. 580 pages; 23.5 × 15.5 cm. 1950. The Williams & Wilkins Company, Baltimore. Price, $8.00.

Gastroscopy: The Endoscopic Study of Gastric Pathology. 2nd ed. By RUDOLF SCHINDLER, M.D., F.A.C.P. 457 pages; 24.5 × 17.5 cm. 1950. University of Chicago Press, Chicago. Price, $20.00.

Haemolytic Disease of the Newborn. By M. M. PICKLES, D.M., Nuffield Graduate Assistant in Clinical Pathology, Radcliffe Infirmary, Oxford. 181 pages; 22.5 × 14.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $4.50.

Handbook of Medical Management. 1st ed. By MILTON CHATTON, A.B., M.D., Instructor in Medicine, University of California Medical School, San Francisco; SHELDON MARGEN, A.B., M.D., Clinical Instructor in Medicine and Research Associate in Medicine, University of California Medical School, San Francisco; and HENRY D. BRAINERD, A.B., M.D., Assistant Clinical Professor of Medicine and Pediatrics, University of California Medical School, San Francisco, etc. 476 pages; 18 × 10 cm. 1949. University Medical Publishers, Palo Alto, California. Price, $3.00.

Helpful Hints to the Diabetic. By WILLIAM S. COLLENS, B.S., M.D., Chief of the Diabetic Clinic, Chief of the Clinic for Peripheral Vascular Diseases, Associate Attending Physician, Maimonides Hospital, etc.; and LOUIS C. BOAS, A.B., M.D., Chief of the Diabetic Clinic, Associate Visiting Physician, Greenpoint Hospital, etc. 135 pages; 23.5 × 15.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $3.00.

Les Ictères: Moyens d'Exploration, Symptômes Physio-pathologie, Thérapeutique. 3d ed. By I. PAVEL. 148 pages; 25 × 16.5 cm. (paper-bound). 1949. Masson et Cie, Paris. Price, 600 fr., "Prix de Vente Obligatoire."

Lipidoses: Diseases of the Cellular Lipid Metabolism. Volume IV, Chapter VII–A. By SIEGFRIED J. THANNHAUSER. 594 pages; 25.5 ×19 cm. (paper cover). 1949. Oxford University Press, Inc., New York.

Medical Diseases of the Kidney (An Atlas and Introduction). By J. F. A. MCMANUS, M.D., Associate Professor of Pathology, The Medical College of Alabama, Bir-

mingham, etc. 176 pages; 26.5 × 17 cm. 1950. Lea & Febiger, Philadelphia. Price, $6.00.

Das Menschliche Knochenmark: Seine Anatomie, Physiologie und Pathologie Nach Ergebnissen der Intravitalen Markpunktion. By PROF. DR. MED. KARL ROHR. 404 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, Ganzleinen DM 47.50.

The Occurrence of Post Infectious Nervous Complications and Allied Disorders in Sweden. (Acta Medica Scandinavica, Supplementum CCXXIV, 224.) By FOLKE MÖLLER. 58 pages; 24 × 17.5 cm. (paper-bound). 1949. Printed by Hakan Ohlssons Boktryckeri, Lund, Sweden.

On Post-Infectious Nervous Involvement and Related Disorders of Spontaneous Origin. (From the cover: "This work also appears as supplementum to Acta Medica Scandinavica.") By FOLKE MÖLLER. 197 pages; 24 × 17.5 cm. (paper-bound). 1949. Printed by Hakan Ohlssons Boktryckeri, Lund, Sweden.

The Origin of Medical Terms. By HENRY ALAN SKINNER, M.B., F.R.C.S. (C.), Professor of Anatomy, University of Western Ontario. 379 pages; 26 × 18 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Primer of Allergy: A Guidebook for Those Who Must Find Their Way Through the Mazes of This Strange and Tantalizing State. 3d ed., revised by J. HARVEY BLACK, M.D. By WARREN T. VAUGHAN, M.S., M.D., Richmond, Virginia. 175 pages; 20 × 13 cm. 1950. The C. V. Mosby Company, Saint Louis. Price, $3.50.

Questions, Medical State Board, and Answers. 8th ed. By R. MAX GOEPP, M.D., Formerly Professor of Clinical Medicine, Graduate School of the University of Pennsylvania, etc., and HARRISON F. FLIPPIN, M.D., Associate Professor of Medicine at the Graduate School of the University of Pennsylvania. 663 pages; 24 × 16 cm. 1950. W. B. Saunders Company, Philadelphia. Price, $7.00.

Recent Advances in Physiology. 7th ed. By W. H. NEWTON, M.D., M.Sc. (Manch.), D.Sc. (Lond.), Professor of Physiology in the University of Edinburgh. 268 pages; 21 × 13.5 cm. 1949. The Blakiston Company, Philadelphia. Price, $4.50.

Stillbirths: Their Epidemiology and Social Significance. By IAN SUTHERLAND, M.A. (Cantab.), D. Phil. (Oxon.), F.S.S., Institute of Social Medicine, Oxford; with a Foreword by JOHN A. RYLE, M.A., M.D., F.R.C.P., Professor of Social Medicine in the University of Oxford. 93 pages; 21.5 × 14 cm. (paper-bound). 1950. Oxford University Press, New York. Price, $1.50.

Streptomycin in the Treatment of Infections. Volume IV, Chapter XXX–C. By CHESTER S. KEEFER, M.D. 44 pages; 25.5 × 19 cm. (paper cover). 1949. Oxford University Press, Inc., New York.

Syphilis. Part II. The Treatment and Prophylaxis of Syphilis. Arsenobismuth, Mercury and Fever Therapy. Volume V, Chapter XXVIII–A. By JOSEPH EARLE MOORE and HARRY EAGLE. *Penicillin Therapy.* By HAROLD A. TUCKER. 33 pages; 25.5 × 19 cm. (paper cover). 1949. Oxford University Press, Inc., New York.

The Toxic and Organic Reaction Types of Mental Disease. Volume VII, Chapter VI. By FRANKLIN G. EBAUGH. 121 pages; 25.5 × 19 cm. (paper cover). 1949. Oxford University Press, Inc., New York.

COLLEGE NEWS NOTES

New Life Members, American College of Physicians

The College is gratified to announce that the following Fellows, in order listed, have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Paul Arthur Burgeson, Warsaw, N. Y.
Benjamin Burroughs Bushong, Traverse City, Mich.
Warner Haines Newcomb, Jacksonville, Ill.
Jacob Joseph Silverman, Staten Island, N. Y.
Gurney Taylor, New York, N. Y.
J. Heyward Gibbes, Columbia, S. C.
Abraham Walter Freireich, Malverne, N. Y.
Fred Gooding Holmes, Phoenix, Ariz.
Will Cook Spain, New York, N. Y.
Henry Pulteney Wright, Montreal, Que., Canada.
Frank B. Lusk, Chicago, Ill.
Delmar Goode, Chevy Chase, Md.
Herman Charles Petterson, Boston, Mass.
Theodore T. Fox, New York, N. Y.
Adolph Matthew Hutter, Fond du Lac, Wis.
Travis Winsor, Los Angeles, Calif.
Frank B. McGlone, Denver, Colo.
Philipp J. R. Schmahl, Mentone, Calif.
Robert Rupen Janjigian, Forty Fort, Pa.
Joseph Franklin Robinson, Wilkes-Barre, Pa.
Valentine Frederick Stock, Toronto, Ont., Canada.
Irving Sherwood Wright, New York, N. Y.
Henry Thomas Smith, McGehee, Ark.
Frank Wright, Chicago, Ill.
F. Garm Norbury, Jacksonville, Ill.
Harry T. French, Hanover, N. H.
Dar Delos Stofer, Monterey, Calif.
Joseph Paul Harvey, Youngstown, Ohio
William Gilmore Leaman, Jr., Philadelphia, Pa.
Oliver Willison Lohr, Saginaw, Mich.
Pat Alexander Tuckwiller, Charleston, W. Va.
Kenneth Paul Hoel, Aurora, Ill.
Harris Vincent Lilga, Petoskey, Mich.
Walter Louis Schafer, Wichita, Kans.
Charles Edward Watts, Seattle, Wash.
Chancel Ray Lounsberry, San Diego, Calif.

The College has an equitable and practicable Life Membership plan whereby members may underwrite their future dues during their productive years, while income is greatest. Life Membership offers security in advancing years against misfortunes which often necessitate the relinquishment of one's most cherished professional memberships because of the burden of dues. All Life Membership fees are added to the permanent Endowment Fund of the College, and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns, thus offering very substantial savings to the subscriber.

A.C.P. Postgraduate Courses

The Preliminary Bulletin of Postgraduate Courses arranged by the American College of Physicians for the Spring and Summer of 1950 was delayed in appearance, awaiting outlines from some of the directors. The detailed outlines of the following courses were not included in the Preliminary Bulletin but separate publications have been issued in the meantime or will be issued in the very near future:

Course No. 4, ELECTROCARDIOGRAPHY: BASIC PRINCIPLES AND INTERPRETATION. Massachusetts General Hospital, Boston, Mass. Conger Williams, M.D., Director. May 8–13, 1950. This course already is greatly oversubscribed by members of the College. The names of those who could not be accommodated have been placed on a waiting list for the next time this course is given.

Course No. 5, ENDOCRINOLOGY. University of Illinois College of Medicine, Chicago, Ill. W. O. Thompson, M.D., F.A.C.P., Director. May 15–20, 1950. Examination of the content of this course shows that it provides an intensive review of recent developments in the field of endocrinology, including endocrine gynecology and sterility. Special attention will be paid to clinical disorders, and physiological and biochemical developments will be presented in relation to their bearing on the interpretation of clinical phenomena. Leading teachers from all over the United States and Canada will participate. Endocrine disorders will be illustrated by presentation of patients. There will be a round table discussion each day at luncheon in which all men on the faculty that day will participate. This will provide an opportunity for the registrants to discuss various problems informally with the teachers. Instead of meeting on the campus of the University of Illinois College of Medicine, all classes will be held in the Illinois Room of the LaSalle Hotel, Chicago. The physical facilities for the course are excellent. Hotel accommodations are available at the La Salle for all registrants.

Course No. 6, THE DYNAMICS OF METABOLIC DISEASES. New York University Post-Graduate Medical School, New York, N. Y. Clarence E. de la Chapelle, M.D., F.A.C.P., Director, and Charles F. Wilkinson, Jr., M.D., Associate Director. May 15–20, 1950. This, a new course on the College schedule, is designed to offer experience, both basic and clinical, in recent developments in the field of internal medicine with emphasis on the diagnosis and treatment of altered metabolic states. The clinical application of the more recent physiological and biochemical advances will be presented by means of seminars. Didactic presentations will be kept to a minimum. The program will be mainly informal, evolved by means of conferences, clinics, seminars and panels with adequate opportunity for participation by the registrants. Entertainment features are also planned.

Course No. 7, TRENDS AND NEWER DEVELOPMENTS IN INTERNAL MEDICINE. Temple University School of Medicine, Philadelphia, Pa. Thomas M. Durant, M.D., F.A.C.P., Director. June 5–10, 1950. This course, also new on the College program, will present in concise fashion many of the trends and newer developments in the rapidly advancing field of Internal Medicine. An entire day will be devoted to Endocrinology and Metabolism and another full day to Diseases of the Gastro-intestinal Tract. Half days will be allotted to Cardiovascular Diseases, Pulmonary Diseases and Antibiotics, Allergy, Hematology, Arthritis, and Neurology and Psychiatry. Case presentations will accompany many of the discussions. Sufficient time will be provided for question and answer periods. Special emphasis will be placed upon those developments in

the various fields which have practical therapeutic application. The "Pituitary-Adrenal Axis" and many of its recently discovered relationships will be included in both the Endocrinology and Arthritis Symposia. Panel discussions will feature several of the symposia. The subjects have been selected with great care, and the faculty will include members of the teaching staffs of near-by medical schools, in addition to those on the faculty of Temple University School of Medicine.

Course No. 9, CLINICAL ASPECTS OF MALNUTRITION. Hospital de Enfermedades de la Nutrición, Mexico, D. F. Salvador Zubiran, M.D., F.A.C.P., Director. August 14–26, 1950. This is an entirely new course on the College schedule. There is probably no institution or group of teachers so well qualified to give a thoroughly practical course in the subject of clinical aspects of malnutrition, because malnutrition is one of the gravest problems in Mexico. Assembled on the faculty will be outstanding authorities from Mexico, all of whom speak English, with two or more outstanding teachers from the United States.

The medical profession of the United States and Canada, interested in this subject, will have an opportunity to learn at first-hand the important strides being made in this field in Mexico. Furthermore, this opportunity will contribute much to the good professional relationships and acquaintanceships of the participating countries. College members, who have taken our postgraduate course in Cardiology in Mexico during 1948 and 1949, were amazed at the facilities and the plane of instruction offered in that country.

The course will cover the fundamental and practical problems of nutrition and should be superior to any course in this field previously offered by the College.

Mexico City is at such an elevation that the climate is delightful and comfortable, even in the midst of summer. There is so much of interest and attraction that the vacation features alone should attract a large number of registrants. Accommodations are available for wives and members of the family.

Among the guest teachers from the United States will be Dr. John B. Youmans, F.A.C.P., heretofore Dean and Professor of Medicine at the University of Illinois College of Medicine, but shortly returning to Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Karver L. Puestow, F.A.C.P., Professor of Clinical Medicine, University of Wisconsin Medical School, Madison, Wis.; and Dr. George R. Herrmann, F.A.C.P., Professor of Medicine, University of Texas Medical Branch, Galveston, Tex.

This course and the attendant vacation opportunities are enthusiastically recommended to the members of the College. Aguirre's Guest Tours, official touring bureau, will arrange every detail, if desired, in regard to entry into and departure from Mexico, hotel reservations, inspection tours, etc.

Course No. 1, CLINICAL ALLERGY, scheduled at the Roosevelt Hospital, New York, N. Y., under Dr. Robert A. Cooke, F.A.C.P., Director, February 6–17, 1950, has been deferred until October 23–November 3, 1950. The full faculty and outline of the course is available in the current Preliminary Bulletin. It is believed that this is the finest available course anywhere in the field of clinical allergy and those interested are encouraged to register long in advance. Instruction, of necessity, must be of a personal type and the number in the class is limited to no more than 8.

Course No. 2, DISEASES OF THE BLOOD VESSELS. Cornell University Medical College and New York Hospital. Dr. Irving S. Wright, F.A.C.P., Director. March 13–18, 1950. This course was new on the College schedule and proved to be one of the most popular and best organized courses ever arranged by the College. The course was registered to full capacity.

Course No. 3, RECENT DEVELOPMENTS IN THE CARDIOVASCULAR FIELD. Michael Reese Hospital Postgraduate School, Chicago, Ill. Dr. Louis N. Katz, F.A.C.P., Director. March 20–25, 1950. This course was greatly oversubscribed by members of the College and no non-members could be accommodated. It is planned to repeat the course in the future.

Course No. 8, INTERNAL MEDICINE. University of California Medical School, San Francisco, Calif. Dr. Stacy R. Mettier, F.A.C.P., Director. June 19–23, 1950. This course has been arranged during the week immediately preceding the Annual Meeting of the American Medical Association, in order that physicians from longer distances may combine the course with attendance at the A.M.A. Meeting. Hotel reservation forms covering not only the period of the course but the meeting of the American Medical Association are available.

The purpose of this course is to present a review of the newer methods of treatment and diagnosis of diseases pertaining to Internal Medicine. The use of new drugs in the treatment of cardiovascular and blood dyscrasia will be emphasized. There will also be a symposium on chemotherapy that will be outstanding in character and will be presented by clinicians who have had broad experience in this field. Finally, a program pertaining to methods of intravascular catheterization for the purpose of diagnosis will be presented.

For registration forms, descriptive folders of courses, etc., consult the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Manitoba and Saskatchewan Regional Meeting

The first annual Regional Meeting of the members of the American College of Physicians for Manitoba and Saskatchewan was held at Winnipeg, February 10, 1950, under the Governorship of Dr. C. H. A. Walton, F.A.C.P. The program was as follows: Sprue Syndrome, J. Wendell MacLeod, M.D., F.A.C.P., Winnipeg; Lecturer in Medicine, University of Manitoba. Coronary Patterns, John M. McEachern, M.D., F.A.C.P., Winnipeg; Assistant Professor of Medicine, University of Manitoba. Management of Obesity, David E. Rodger, M.D. (Associate), Regina; Director of Medicine, Medical Arts Clinic. Enlarged Middle Cranial Fossa—Report of Cases, Sidney Israels, M.D. (Associate), Winnipeg. Fundamental Considerations in Anticoagulant Therapy, L. B. Jaques, Ph.D. (by invitation), Professor of Physiology, University of Saskatchewan, Saskatoon. Bronchogenic Carcinoma, John D. Stenstrom, M.D. (by invitation), Victoria, B. C. ACTH and Cortisone in Various Diseases, J. S. L. Browne, M.D., F.A.C.P., Montreal, Que.; Professor of Medicine, McGill University. A dinner was held at the Manitoba Club for members of the College and guests. Speaker of the day was Maurice C. Pincoffs, M.D., M.A.C.P., Assistant to the President for Medical Affairs, University of Maryland, and Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.

Nebraska Regional Meeting

The annual Regional Meeting for Nebraska was held in Lincoln, February 11, 1950, under the Governorship of Dr. J. D. McCarthy, F.A.C.P., of Omaha, and the Program Chairmanship of Dr. George W. Covey, F.A.C.P., of Lincoln. 53 members and 18 non-members were in attendance. This represents a large proportion of the members in the state. There were but 14 not heard from in connection with the meeting.

Dr. William S. Middleton, F.A.C.P., President-Elect of the College, Madison, Wis., was the guest of honor and presented on the scientific program a paper entitled "Moot Points in Cardiac Therapy" and addressed the banquet meeting in the evening on "The Inquiring Mind." The rest of the program was as follows: Dissecting Aneurysm of Aorta Simulating Acute Myocardial Infarction, Arthur L. Smith, Jr., M.D. (Associate), Lincoln. Hand-Christian-Schuller Disease: Report of a Case, Harold C. Lueth, M.D., F.A.C.P., Omaha and William E. Graham, M.D. (by invitation), Omaha; Resident in Internal Medicine, University of Nebraska Hospital. Ewing Tumor of Bone, J. Marshall Neely, M.D., F.A.C.P., Lincoln. Aureomycin in the Treatment of Amebiasis, Horace H. Zinneman, M.D. (Associate), Lincoln, and Charles Gutch, M.D. (by invitation), Lincoln. Progress in Heart Sound Analysis, F. Lowell Dunn, M.D., F.A.C.P., Omaha. Hemochromatosis without Glycosuria: A Case Report with Autopsy Findings, Sanford M. Rathbun, M.D. (Associate), Beatrice. Disseminated Fungus Infections: Reports of Three Cases with Autopsy Findings, O. V. Calhoun, M.D., F.A.C.P., and Orest J. Parrillo, M.D. (by invitation), Lincoln.

Colorado Regional Meeting

The annual Colorado Regional Meeting was held at Denver on February 21, 1950, under the Governorship of Dr. Ward Darley, F.A.C.P., and the States of Idaho, New Mexico, Montana and Wyoming coöperated through their respective Governors, Dr. Samuel M. Poindexter, F.A.C.P., Boise, Dr. Walter I. Werner, F.A.C.P., Albuquerque, and Dr. Harold W. Gregg, F.A.C.P., Butte. Dr. Louis S. Faust, F.A.C.P., of Denver, was Chairman of the Program Committee, and the program was as follows: Welcome Address, Ward Darley, M.D., F.A.C.P. Adams-Stokes Attacks Due to Ventricular Fibrillation in a Heart Essentially Normal Anatomically, Hope Lowry, M.D. (Associate), and Edna Stuver, M.D. (by invitation), Denver, Colo. The Incidence of Heart Disease in University Students, Stella H. Sikkema, M.D. (Associate), Margery Shearer, M.D. (by invitation), and Lawrence W. Holden, M.D., F.A.C.P., Boulder, Colo. Use of Dicumarol in Congestive Heart Failure, Robert W. Truscott, M.D. (by invitation), Denver, Colo. Myocardial Involvement in Infectious Mononucleosis, H. Alexander Bradford, M.D., F.A.C.P., Denver, Colo. The Effect of Imbalance of the Autonomic Nervous System on the Electrocardiogram, C. P. Stevenson, M.D. (Associate), and S. C. Percefull, M.D. (by invitation), V. A. Hospital, Fort Logan, Colo. The Use of Digitalis in Cardiac Disease in the Absence of Congestive Heart Failure or Auricular Fibrillation, Ferdinand R. Schem, M.D., F.A.C.P., Great Falls, Mont. Diagnosis: Psychoneurosis—What Happens Now? John M. Lyon, M.D. (Associate), Denver, Colo. The Collagen Diseases, William S. Middleton, M.D., F.A.C.P., President-Elect, American College of Physicians; Dean, University of Wisconsin Medical School; Madison, Wis. Report on Results of the Treatment of Addison's Disease by the Implantation Method (Presentation of Cases), C. F. Kemper, M.D., F.A.C.P., Denver, Colo. Evaluation of Round Lesions of the Lung, John B. Grow, M.D. (by invitation), Denver, Colo. Recent Advances in Pulmonary Resections in the Treatment of Pulmonary Tuberculosis, James H. Forsee, Sr., Colonel, (MC), F.A.C.P., and C. W. Tempel, Colonel, (MC), F.A.C.P., Fitzsimmons General Hospital, Denver, Colo. Blood Volume Measurements in Polycythemia, Joseph H. Holmes, M.D. (Associate), Denver, Colo. A dinner meeting was held at the Shirley-Savoy Hotel for members of the American College of Physicians, Medical Society of the City and County of Denver, and Midwinter Clinics Group. Guest of honor and speaker was William S. Middleton, M.D., F.A.C.P., President-Elect, American College of Physicians; Dean, University of Wisconsin Medical School; Madison, Wis. Dr. Middleton spoke on "The Physician and the Cardiac Patient."

Virginia Regional Meeting

The annual Regional Meeting of the American College of Physicians for Virginia was held at Richmond, Wednesday, February 22, 1950, under the Governorship of Dr. J. Edwin Wood, Jr., F.A.C.P., and the Program Chairmanship of Dr. Charles M. Caravati, F.A.C.P. In Virginia there is a formal organization of the members of the College, and Dr. Douglas G. Chapman, F.A.C.P., Richmond, is Chairman, and Dr. James F. Waddill, F.A.C.P., Norfolk, is the Secretary-Treasurer. The program was as follows: The Leukemoid Reaction: Report of Case, Joseph R. Kriz, M.D., F.A.C.P., and Kinloch Nelson, M.D. (Associate), Richmond, Va. The Shoulder-Hand Syndrome Associated with Coronary Insufficiency and Thrombosis, Elam C. Toone, Jr., M.D., F.A.C.P., and Oscar W. Clarke, M.D. (by invitation), Richmond, Va. The Serum Amylase Response to Morphine, Mecholyl, and Secretin, James O. Burke, M.D. (Associate), and Kemp Plummer, M.D. (by invitation), Richmond, Va. Sympatholytic Drugs in Peripheral Vascular Disease, Nathan Bloom, M.D., F.A.C.P., Richmond, Va. Ventricular Tachycardia Complicating Myocardial Infarction: Case Report with Particular Reference to Therapy, John B. McKee, M.D., F.A.C.P., Winchester, Va. Primary Systemic Amyloidosis: Report of Case, William H. Higgins, M.D., F.A.C.P., and William H. Higgins, Jr., M.D. (by invitation), Richmond, Va. Esophageal Tamponade: Report of Cases, J. M. MacMillan, M.D., F.A.C.P., and C. M. Caravati, M.D., F.A.C.P., Richmond, Va. Electro-shock in Patients with Cardiovascular Disease, J. A. Shield, M.D. (Associate), and Howard M. McCue, M.D. (by invitation), Richmond, Va. Agnogenic Myeloid Metaplasia, Gilman R. Tyler, M.D., F.A.C.P., and Jean F. Wine, M.D. (by invitation), Richmond, Va. Epicardial Constricting Pericarditis, William B. Porter, M.D., F.A.C.P., and R. A. Adams, M.D. (by invitation), Richmond, Va., and S. B. Alexander, M.D. (by invitation), Chapel Hill, N. C. Low Renal Threshold in Diabetics, W. R. Jordan, Sr., M.D., F.A.C.P., Richmond, Va. Congenital Heart Disease: Report of Case, P. D. Camp, Jr., M.D., F.A.C.P., Richmond, Va. Sheehan's Disease (Postpartum Pituitary Failure): Case Report, H. St. George Tucker, Jr., M.D. (Associate), J. P. Lynch, M.D., F.A.C.P., and Isabel Taliaferro, M.D. (by invitation), Richmond, Va.

Maryland—District of Columbia—Delaware Regional Meeting

The Annual Regional Meeting for Maryland, the District of Columbia and Delaware was held in the Hurd Memorial Hall of Johns Hopkins Hospital at Baltimore on February 25, 1950, under the Governorship of Dr. Wetherbee Fort, F.A.C.P., and the General Chairmanship of Dr. R. Carmichael Tilghman, F.A.C.P., and with the coöperation of the Governors of the District of Columbia and Delaware, Dr. John Minor, F.A.C.P., Washington, and Dr. Lemuel C. McGee, F.A.C.P., Wilmington, respectively. The program follows: Current Trends in the Use of Chemotherapeutic Agents and Antibiotics in Pulmonary Tuberculosis, Monroe J. Romansky, M.D., F.A.C.P., and Sol Katz, M.D., F.A.C.P., Washington, D. C. The Use of Hypotensive Agents and Diet in the Treatment of Severe Essential Hypertension, Edward H. Fries, M.D. (by invitation), Washington, D. C. The Treponemal Immobilizing Antibody and Its Implications in the Immunology of Syphilis, Robert A. Nelson, Jr., M.D. (by invitation), Baltimore, Md. Panel—Peptic ulcer: *Moderator*, Sara M. Jordan, M.D., F.A.C.P., Boston, Mass. *Internal Medicine*, Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, Md. *Surgery*, George G. Finney, M.D., F.A.C.S. (by invitation), Baltimore, Md. *Psychiatry*, Jacob E. Finesinger, M.D. (by invitation), Baltimore, Md. *X-Ray*, Robert P. Barden, M.D. (by invitation), Philadelphia, Pa. Clinical Observations with ACTH and Cortisone, A. McGehee Harvey, M.D., F.A.C.P., Baltimore, Md. Preliminary Report on a Treatment in Tuberculosis, Robert H. Siver, M.D.

(Associate), Baltimore, Md. Sudden Death, Russell S. Fisher, M.D. (by invitation), Chief Medical Examiner, State of Maryland. Adrenal Insufficiency in Childhood with Characteristic Electrocardiographic Changes, Lawrence Kyle, M.D. (by invitation), Washington, D. C. Handling Disturbances in Potassium Metabolism in the General Hospital, J. Richard Durham, Jr., M.D., F.A.C.P., Wilmington, Del. Rôle of Sodium Studies in the Therapy of Cirrhosis of the Liver, William Eisenmenger, M.D. (by invitation), New York, N. Y. Insulin Insensitivity in Diabetes Mellitus: Implications and Approaches to Management, Hyman J. Zimmerman, M.D. (associate), and Alvin E. Parrish, M.D. (by invitation), Washington, D. C. Mitral Stenosis—Its Surgical Treatment by Commissurotomy, Charles P. Bailey, M.D., F.A.C.S. (by invitation), Philadelphia, Pa.

Kansas Regional Meeting

The annual Regional Meeting of the American College of Physicians for Kansas was held at Topeka, March 17, 1950. The current meeting was held under the Governorship of Dr. William C. Menninger, F.A.C.P., Topeka, and the Program Chairmanship of Dr. Nathaniel Uhr, F.A.C.P., Topeka. The Kansas Regional Meeting was initiated some years ago under Dr. Harold H. Jones, of Winfield, Kans., former Governor of the College, and they have become outstanding meetings in that state. The program this year was as follows: *Chairman*, Morning Sessions: Fred J. McEwen, M.D., F.A.C.P., Wichita, Kans. Problems in Cardiovascular Syphilis, Max S. Allen, M.D (by invitation), Kansas City, Kans. The Effect of Human Albumin on Hepatomegaly of Cardiac Origin; A Preliminary Report, G. L. Norris, M.D. (Associate), Winfield, Kansas. Hemolytic Anemia Associated with Ovarian Teratoma; Report of Two Cases, H. Alden Flanders, M.D. (by invitation), Hays, Kans. Clinicopathological Conference, Alfred Plaut, M.D. (by invitation), Pathologist, Winter Veterans Administration Hospital, Topeka, Kans. *Chairman*, Afternoon Session: Franklin D. Murphy, M.D., F.A.C.P., Kansas City, Kans. Exogenous Hemochromatosis Following Multiple Blood Transfusions; a Case Report, Robert P. Norris, M.D. (by invitation), and Fred J. McEwen, M.D., F.A.C.P., Wichita, Kans. Problems in Psychosomatic Medicine, Sidney Rubin, M.D. (Associate), Winter Veterans Administration Hospital, Topeka, Kans. Experiences with Stilbamidine in the Treatment of Multiple Myeloma, Robert S. Wallerstein, M.D. (by invitation), and Gerald A. Reeves, M.D. (by invitation), Topeka, Kans. Coagulability of the Circulating Blood Following Operation, J. L. Morgan, M.D. (by invitation), Emporia, Kans. Hypogonadism in the Adult Male, William T. Sirridge, M.D. (by invitation), Kansas City, Kans. Guest speaker at the dinner was Hugh J. Morgan, M.D., F.A.C.P., Professor of Medicine, Vanderbilt University, Nashville, Tenn.; recently President and currently Regent of The American College of Physicians. Special Guests included Ward Darley, M.D., F.A.C.P., Governor for Colorado, American College of Physicians; Ralph A. Kinsella, M.D., F.A.C.P., Governor for Missouri, American College of Physicians; Wann Langston, M.D., F.A.C.P., Governor for Oklahoma, American College of Physicians; J. D. McCarthy, M.D., F.A.C.P., Governor for Nebraska, American College of Physicians.

Biographical Correction 1949 Directory, A.C.P.

Dr. Aaron E. Parsonnet, F.A.C.P., Newark, N. J., is Attending Physician at the Newark Beth Israel Hospital, not an Assistant Physician as indicated in the text of the College Directory. (Editorial Correction.)

Postgraduate Courses Offered by University of California Extension

The School of Medicine and University Extension of the University of California has announced the following postgraduate courses:

INFECTIOUS DISEASES OF VIRAL AND RICKETTSIAL ORIGIN —Tuesday evenings, 8:00–10:00 p.m., February 14–April 11, 1950. No fee.

GENERAL SURGICAL PATHOLOGY REVIEW—Saturday mornings, 9:00 a.m.–1:00 p.m., March 4–April 22, 1950. Fee $75.00.

THE RADIOISOTOPES AND THEIR USE IN CLINICAL MEDICINE —Wednesday evenings, 8:00–10:00 p.m., March 15–April 19, 1950. Fee, $25.00.

Applications for enrollment or requests for information should be made to the Office of Medical Extension, University Extension, University of California, Los Angeles 24, Calif.

Postgraduate Course in Pulmonary Diseases and Their Relation to Employment

The American Trudeau Society announces a postgraduate course in Pulmonary Diseases, patterned after the type of postgraduate course given by the American College of Physicians, to be given at Pittsburgh, Pa., May 15–19, 1950, especially for physicians residing in Pennsylvania, New Jersey, New York, Delaware, and the Provinces of Quebec and Ontario, Canada. This does not mean, however, that physicians from other states and other parts of Canada may not be accepted, but the American Trudeau Society attempts to give courses in various parts of the United States and this particular region is best served by this course. Classes will meet at the University Club and the course is given in coöperation with the University of Pittsburgh School of Medicine and Graduate School of Public Health and Industrial Hygiene Foundation of America. Dr. C. Howard Marcy, F.A.C.P., is the Director. Registration fee: $50.00. For application blanks and full details, address the American Trudeau Society, 1790 Broadway, New York 19, N. Y.

Trudeau School of Tuberculosis Postgraduate Courses

The Trudeau School of Tuberculosis, Saranac Lake, N. Y., will conduct a postgraduate course for graduates in medicine who wish to prepare themselves for sanatorium or public health service and for physicians who desire a refresher course in tuberculosis, at Saranac Lake, May 1–27, 1950. The program aims to present the essentials of history, etiology, epidemiology, pathology, diagnosis, prognosis and treatment. The fee is $100.00. Information is available through the Secretary, Trudeau School of Tuberculosis, P. O. Drawer 131, Saranac Lake, N. Y.

This School was founded in 1916. In the meantime there have been from 800 to 900 graduates who have come from every state in the Union and from many foreign countries. Classes are limited to 35. The course covers not only tuberculosis but other diseases of the chest.

U. S. Public Health Service Course Schedule Revised

The schedule of Public Health Laboratory Courses given by the Communicable Disease Center, 291 Peachtree St., N. E., Atlanta, Ga. for 1950 is revised as follows:

An additional one-week course in Laboratory Diagnosis of Enteric Diseases, Introductory Enteric Bacteriology, will be given March 20–24, 1950.

An additional two-week course in Laboratory Diagnosis of Tuberculosis will be given December 4–15, 1950.

The previously announced three-week course in the Laboratory Diagnosis of Tuberculosis will be given August 21–September 7, 1950, instead of the dates previously announced.

An additional one-week course in Serological Diagnosis of Rickettsial Diseases will be given November 6–10, 1950.

Army Medical Library Solicits Portraits of Eminent Physicians

The Army Medical Library has resumed solicitation of portraits of persons prominent in Medicine and its related fields. Prior to World War II this program was initiated and the photographs of numerous Fellows and Masters of the American College of Physicians were obtained. The Library expects soon to address requests for portraits to Fellows and Masters of this College and they have already done so in the case of the American College of Surgeons. The Library would also be pleased to receive portraits of physicians not directly solicited. Unmounted glossy prints, autographed and approximately 8×10 inches in size, are preferred, with the name of the subject and the year the photograph was taken on the reverse. They should be addressed to the Catalog Division, Army Medical Library, Washington 25, D.C.

Army Medical Library's Index-Catalogue to Be Changed

A revision of the Army Medical Library's plans for the publication of medical indexes toward a system more in keeping with modern medical indexing requirements will be made in the near future, according to an announcement by Major General R. W. Bliss, the Army Surgeon General. *The Index-Catalogue of the Library of the Surgeon General's Office* will be brought up to date with a volume or volumes to make the record of its monographic holdings complete up to the mid-century mark, and to publish selectively the most useful portion of the yet unpublished subject references that have accumulated. Provisions for a continuing record of the Library's monographic holdings have been assured in the form of an annual supplement to the Library of Congress Catalog of Printed Cards.

At the same time, the Library's *Current List of Medical Literature* will be augmented and made to include an author index; a standard list of journals to be covered regularly will be introduced, and a cumulative subject index will be provided. The rich and vast resources of the Library as a center of historical research will continue to be at the disposal of medical scholars everywhere.

A Prize Essay Award has been announced by the American College of Chest Physicians. A prize of $250.00 will be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease. The prize is open to contestants of foreign countries as well as those residing in the United States. The winning contribution will be selected by a board of impartial judges, and the first award will be made at the annual meeting of the College to be held in San Francisco, June 22–25, 1950.

The following conditions must be observed:

(1) Five copies of the manuscript, typewritten in English, should be submitted to the office of the American College of Chest Physicians not later than May 1, 1950.

(2) The only means of identification of the author or authors shall be a motto or other device on the title page and a sealed envelope, bearing the same motto on the outside, enclosing the name of the author or authors.

Additional information may be obtained from the Executive Secretary of the College, 500 North Dearborn Street, Chicago 10, Ill.

Announcement of Regular Corps Examination for Medical Officers United States Public Health Service

A competitive examination for appointment of Medical Officers in the Regular Corps of the United States Public Health Service will be held on May 15, 16, and 17, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to the homes of candidates. Applications must be received no later than April 17, 1950.

Appointments will be made in the grades of Assistant Surgeon and Senior Assistant Surgeon. All appointments are to the general service and are subject to change of station and assignment as necessitated by the needs of the Service, although consideration is given to the officer's preference, ability and experience. Appointments are permanent in nature and provide opportunities to qualified physicians for a life career in clinical medicine, research and public health.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. Attention: Division of Commissioned Officers.

The Research Division of Harper Hospital, Detroit, Mich., has announced the grant of $10,000 from the United States Public Health Service, National Institute of Health, Division of Medical Research Grants, to Louis A. Schwartz, M.D., F.A.C.P., for a research study to be made on the "Psychosomatic Aspects of Peptic Ulcer."

The Oklahoma State Heart Association was recently formed in Oklahoma City. Dr. Homer A. Ruprecht, F.A.C.P., was elected president, with Dr. W. W. Rucks, Jr., F.A.C.P., vice president; Dr. Robert H. Bayley, F.A.C.P., secretary; and Dr. Wann Langston, F.A.C.P., Governor for Oklahoma, chairman of the board. The association will later be affiliated with the National Heart Association, and a three-fold program of research, education and community service will be sponsored.

At the annual meeting of the American Goiter Association held in Houston, Texas, March 9–11, Dr. Samuel F. Haines, F.A.C.P., Rochester, Minnesota, president of the Association, delivered an address on the "Influence of Research on the Modern Treatment of Exophthalmic Goiter."

Dr. Tom D. Spies, F.A.C.P., Professor of Nutrition and Metabolism and chairman of the department at Northwestern University Medical School, Chicago, and Robert R. Williams, Sc.D., formerly chemical director of the Bell Telephone Laboratories in New York, received the Orden de Carlos Manuel de Cespedes decoration, the highest award of the Cuban government, January 23, in Havana. Dr. Spies was honored for his contribution to the field of nutritional deficiency diseases. The Orden de Carlos Manuel de Cespedes decoration was created in 1926 in honor of Carlos Manuel de Cespedes, first president of Cuba, and is given to a Cuban or a foreigner who has done outstanding work of a humanitarian nature for the Cuban people.

Dr. Gilbert M. Stevenson, F.A.C.P., Governor of the College for Panama and the Canal Zone, was recently honored by election to the Panamanian Academy of Medicine and Surgery as a foreign corresponding member.

Dr. William J. Kerr, F.A.C.P., Professor of Medicine at the University of California Medical School, was recently honored by the *American Practitioner* in designating its December 1949 issue as a memorial volume on the occasion of his sixtieth birthday. Dr. Kerr served as President of the American College of Physicians in 1938–39.

The Commission on Graduate Education of The Medical Society of the State of Pennsylvania, 230 State Street, Harrisburg, Pa., announces a Special Electrocardiography Course to be held in the Nurses' Auditorium, Harrisburg Hospital, on Thursdays, May 11, 18, 25, June 1, 8, 15, and 22, 1950. Registration fee is $35.00. Additional information and applications may be obtained by writing to the Commission.

Dr. Seymour H. Rinzler, F.A.C.P., Instructor in Rehabilitation, New York University College of Medicine, has been selected as the winner of the 1949 Essay Contest conducted by the Mississippi Valley Medical Society. Dr. Rinzler's essay was on the subject, "Present Status of Medical and Surgical Therapy in Angina Pectoris," which was published in the January 1950 issue of the *Mississippi Valley Medical Journal*.

Dr. Harry M. Kandel, F.A.C.P., Savannah, was elected President of the Georgia Medical Society at the Society's annual meeting held in Savannah on December 13. Dr. John L. Elliott (Associate), Savannah, was elected a delegate at the same time.

For the best paper presented before the First Inter-American Congress on Industrial Hygiene, Col. Wesley C. Cox, (MC), Chief of the Army Industrial Hygiene Laboratory, received a gold medal on December 14, 1949, in Buenos Aires. The presentation was made by Gen. Juan Peron, President of the Argentine Republic. Col. Cox's paper traced the development of governmental industrial hygiene in the United States from about 1912 until the recent national emergency.

Dr. Paul R. Hawley, F.A.C.P., was appointed Director of the American College of Surgeons, effective March 1, 1950. Dr. Hawley resigned his previous post as Chief Executive Officer of the Blue Cross and Blue Shield Commissions on January 3, having held this position since April 1, 1948. Previous to the Blue Cross-Blue Shield appointment Dr. Hawley was Chief Medical Director of the Veterans Administration.

Dr. Malcolm T. MacEachern, F.A.C.P., who resigned as Director of the College of Surgeons, will devote most of his time in the future to supervising the hospital activities of the College.

At the Annual Alumni Day of Cornell University Medical College held on March 23, 1950, the second annual award to an alumnus for outstanding contributions to medicine was conferred on Dr. David P. Barr, F.A.C.P., Professor of Medicine at Cornell University Medical College.

Dr. Cleve C. Odom, F.A.C.P., has been appointed superintendent of the South Carolina State Hospital and director of the South Carolina state mental hygiene activity. Dr. Odom was formerly manager of the Veterans Administration Hospital, Augusta, Ga.

The Medical College of Virginia has announced the promotion of Dr. Elam C. Toone, Jr., F.A.C.P., from Assistant to Associate Professor of Medicine, and also the appointment of Dr. Joseph R. Kriz, F.A.C.P., as Associate Professor of Pathology in addition to being Assistant Professor of Clinical Pathology.

Under the auspices of the Postgraduate Program for House Officers of the University of Virginia, Department of Medicine, Dr. Reginald Fitz, President of the American College of Physicians, and Assistant Dean of Medicine, Harvard Medical School, addressed the student body and faculty on the subject, "Birdseye View of Medical Education."

Dr. W. H. H. Turville, F.A.C.P., recently retired from the Medical Corps, U. S. Navy, with the rank of Captain, presently is Assistant Director of the Division of Tuberculosis and Sanatoria of the Massachusetts Department of Public Health with headquarters in the State House, Boston. Dr. Turville is expected shortly to be promoted to Director of Hospital Survey and Construction for the State.

Dr. Raymond Hussey, F.A.C.P., formerly connected with the School of Occupational Health in Detroit, has joined the headquarters staff of the American Medical Association as Scientific Director of the Council on Industrial Health. His activities will include the areas of interest having to do with the Research Development, Education and Workman's Compensation.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was an invited guest speaker before the Puerto Rico Medical Association's 46th Annual Assembly at San Juan. On the trip, Dr. Goldstein also gave two lectures at the University of Santo Domingo Medical School and three lectures at the University of Havana School of Medicine.

OBITUARIES

DR. SAMUEL REESE HAYTHORN

Samuel Reese Haythorn, M.D., F.A.C.P., died in Pittsburgh on December 6, 1949, after a brief illness. He was born on September 10, 1880, in Danville, Illinois, and received his degree in medicine from the University of Michigan in 1904. He served as assistant in Pathology under the late Dr. Aldred S. Warthin for two years, following which he obtained additional graduate training in Boston as assistant in Pathology at the Boston City Hospital and at the Harvard Medical School under the leadership of the late Dr. Frank B. Mallory. In 1910 he was appointed Instructor in Pathology at the University of Pittsburgh, and later Assistant Professor. He was appointed Pathologist to the Allegheny General Hospital in 1913, which position he held until 1921 when he was recalled to the University of Pittsburgh as Professor of Pathology and Bacteriology. In 1926 he returned to the Allegheny General Hospital as Director of the William H. Singer Memorial Research Laboratory, which position he held until his death. He was a Fellow of the American College of Physicians since 1920.

Dr. Haythorn was a member of numerous local and national societies and Past President of the American Association of Pathologists and Bacteriologists, the Society of Experimental Pathology, International Association of Medical Museums, the Pittsburgh Academy of Medicine and the Allegheny County Medical Society. He served on the Board of Trustees of the latter society for the period of 12 years prior to his death. He was a Diplomate of the American Board of Pathology.

Dr. Haythorn was widely known for his investigations and numerous publications in the specialty of Pathology. He was an enthusiastic teacher, an indefatigable worker, a precise experimentalist and an inspiration to a host of younger physicians who received graduate training under his supervision, several of whom remain in the specialty of Pathology. His professional influence will remain active for years to come and his numerous friends and colleagues will long remember his spirited humor, kindliness, loyalty and wisdom.

ELWYN L. HELLER, M.D.

DR. EDMUND C. BOOTS

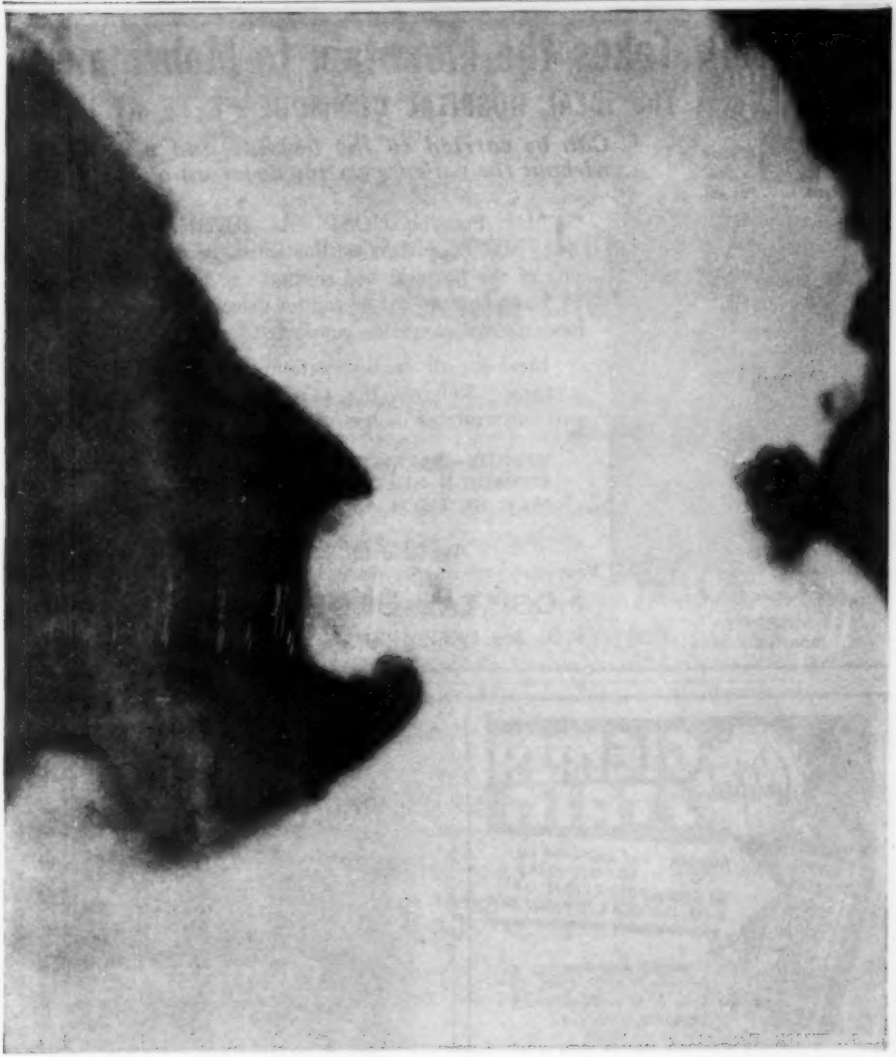
Dr. Edmund C. Boots, F.A.C.P., Pittsburgh, died December 24, 1949, of coronary occlusion.

He was born at New Brighton, Pa., February 14, 1894, graduated from the University of Pittsburgh School of Medicine in 1920, interned at the St. Francis Hospital, Pittsburgh, 1920–21, and served two years' residency at St. Margaret's Hospital, Pittsburgh.

He specialized in Internal Medicine and was a Diplomate of the American Board of Internal Medicine. He was a member of the Senior Staff of Columbia Hospital, Wilkinsburg, Pa.; Supervisor of the Medical Department of the Pittsburgh Board of Education; Medical Consultant, Allegheny County Home, Woodville, Pa., and was a member of the Allegheny County Medical Society, the Pennsylvania State Medical Association, the American Medical Association, the American School Health Association, American Heart Association, American Diabetic Association, American College of Chest Physicians, and had been a Fellow of the American College of Physicians since 1942.

Throughout his professional life Dr. Boots was interested in health education and devoted a great part of his time to this field. He was a man greatly admired by his professional colleagues and the community in which he practiced. He will be missed by all.

CHARLES W. MORTON, M.D., F.A.C.P.,
Governor for Western Pennsylvania



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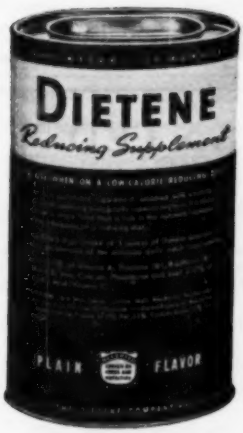

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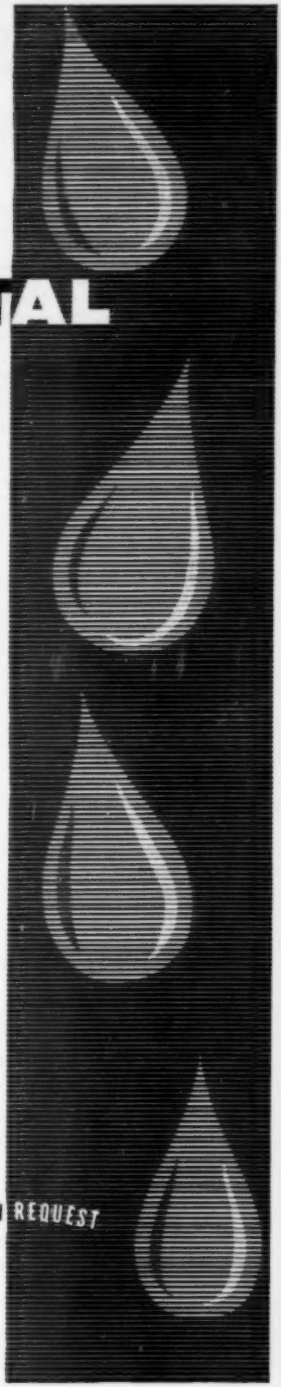

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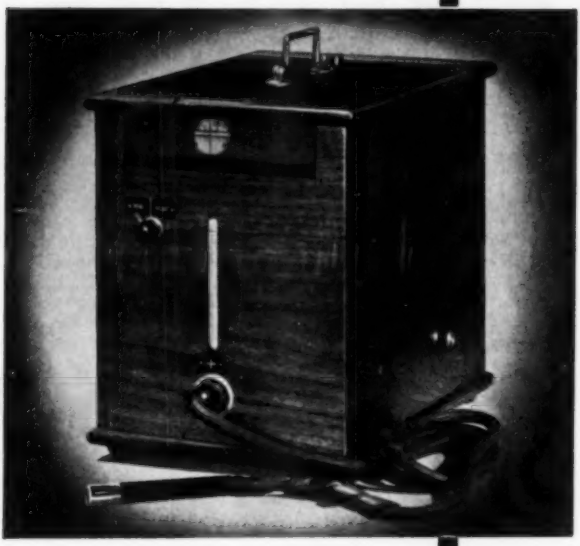

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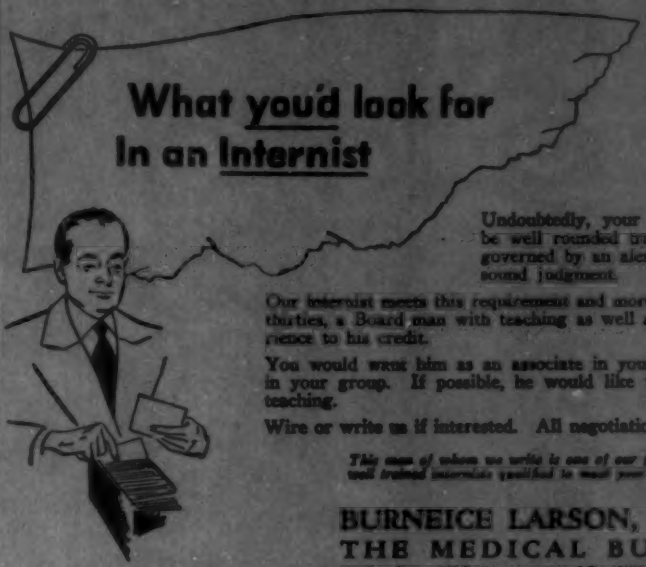

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